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STUDIES ON THE CEREBROSP INAL FLUID

FRANK C. BECHT

From Hull Physiological Laboratory, the University of Chicago, and from the Department of Pharmacology, Northwestern University

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I. A CRITICAL STUDY OF THE METHODS EMPLOYED IN THE OBSERVATIONS ON THE CEREBROSPINAL FLUID

Introduction

Recent publications regarding the formation of the cerebrospinal fluid have been so numerous and at first glance so complete and carefully controlled, that further work on the subject should be unnecessary. To many this seems to constitute a completed chapter in physiology, for they believe that it has been established definitely and clearly that the cerebrospinal fluid is formed by a secretory process, and that this process is capable of stimulation and inhibition by substances of plant and animal origin. However, the fact that some important mechanical factors have been disregarded by some and under-estimated by others, justifies us in the publication of a paper embodying the results of our experiments. We wish to introduce in considerable detail the data from our work—a procedure followed by none of our recent predecessors in the field—so the reader may satisfy himself in regard to the number of experiments, the results, and the variations between experiments where variations existed.

General statement of the problem

An analysis of the problem involved and a review of the literature covering the formation of the cerebrospinal fluid, show that the subject divides naturally into two sections: The study of the actual separa-

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tion of the fluid from the blood or lymph, and the laws governing the process; and the study of the movement of the fluid lying free in the sub-arachnoid space and its communicating cavities. This latter study is a complex one, because the fluid may or may not be retained in the various recesses of the subdural spaces and the central canal when the attempt is made to drain out the pre-formed fluid, or to collect that newly formed. Besides, to that already present more may be added by new formation, or from it some may be removed by absorption along the natural channels. Writers on this subject have not discriminated with sufficient care between these two phases. Many may have been studying the movements of the fluid while assuming that they were studying the formation of the fluid. This, together with the fact that conclusions are sometimes given instead of experimental data, and that no mention is made of the number of experiments or of the limits of variations between experiments, leaves the reader much in doubt regarding the truth of the situation in the study of the formation of the cerebrospinal fluid.

Critical review of the status of the formation of cerebrospinal fluid

The first problem—the study of the actual separation of the fluid and the mechanism involved—has never been solved sufficiently to warrant a definite statement regarding even the structure concerned in the formation. Thus the mechanism of the separation must of necessity have remained untouched. The general consensus of opinion regarding the process is that it is a secretory one, an idea advocated first by Faivre in 1853 (1). The secretory theory was held to be supported by the observation made by Cappelleti (2) that pilocarpine and other drugs usually considered secretogogues increased the amount of fluid which escaped from a temporary or permanent fistula made into the dural canal. The direct evidence that the process is secretory, and that the choroid plexus is concerned in the process is purely anatomical. Petit and Girard (3) described changes in the cells of the choroid plexus after secretory drugs, particularly after pilocarpine and muscarine, changes which were interpreted as evidences of secretion. This work was confirmed and extended by Meek (4). To quote from the latter author:

In the case of the rabbit and the guinea pig muscarine produces decisive results.

Often as many as two-thirds of the cells show evidence of secretion. Normally the epithelial cells in the rabbit are six micra high, but here the height has increased to twelve micra. A differentiation into two zones, a basal granular and an outer clear zone is suggested, but is not so well marked as in the figures of Petit and Girard. The granulation, however, is always heavier and more compact toward the base of the cell. Clear spaces begin to appear toward the top, and rarely does the stainable cytoplasm extend to the upper cell wall. Masses of larger granules are common in the upper part of the cell, where the lines forming the reticulations cross. The nucleus remains globular with a clear outline, in fact it is not distinguishable from that of the resting cell. The two things most striking about these modified cells are their increase in height and the appearance of so much clear space at the distal side of the nucleus.

If we turn now to the work of Langley (5), we find the following (p. 263) regarding the parotid gland of the rabbit:

The alveoli of the parotid of a hungry rabbit taken fresh from the animal and at once examined are granular throughout; there is no division into an outer clear and an inner granular zone. . . . . But if the gland be thrown for some time into a state of activity either by stimulating the sympathetic in the neck, or by injecting pilocarpine, or by feeding, the alveoli alter their appearance and instead of being granular throughout become clear at their outer portion near the basement membrane, and thus show an inner granular and an outer clear, non-granular, zone. . . . . The longer the gland is stimulated the more obvious the outer clear zone becomes, so that at length some alveoli may show scarcely any granules. . . . . The cells, too, ... become smaller . . . . at the same time such nuclei as were irregular, or were compressed become spherical, and move somewhat toward the center of the cell . . . . (p. 279). In the mucous glands during secretion the changes in life are less readily followed, but they are probably similar to those mentioned above. In activity the granules are used up, and disappear first from the peripheral parts of the cell. . . . . The infraorbital and lachrymal glands show an outer clear and an inner granular zone in activity, even more distinctly than the parotid.

A comparison of these statements leads one to suspect some error. In the case of the parotid and other glands examined by Langley, resting cells are granular throughout, and during activity become *smaller*, the cytoplasm is differentiated into an *inner* (i.e., toward the free edge) *granular* and an *outer* (basal) *clear* zone, and the *nuclei become less distorted* and move toward the center of the cell. In the case of the choroid plexus the resting cells are granular throughout; during activity the cells become *larger*—at least they are doubled in height, the cytoplasm is differentiated into an *outer* (i.e., toward the free edge) *clear* and an *inner* (basal) *granular* zone and the *nucleus cannot be differentiated* from the nucleus of the resting cell. Here, then, are changes in two structures, changes, so far as can be determined from reading

the accounts, exactly opposite in character, yet both are considered evidences of physiological activity, and what is more puzzling as evidences of the same activity, viz., of secretion.

It is, therefore, evident that while anatomical changes are produced in the choroid plexus by the action of drugs commonly producing secretion, such as muscarine and pilocarpine, the significance of this change is one of interpretation only, and more than one interpretation is possible. Instead of considering that this change described in the choroid means secretion, one might with equal right assert that from the anatomical evidence the choroid plexus is an organ of absorption of the cerebrospinal fluid as shown by the increased height of the cells.

From the physiological side we have some experiments which bear on the general seat of formation of the fluid. Dandy and Blackfan (6) apparently were the first to produce artificial internal hydrocephalus. They occluded the aqueduct of Sylvius by introducing a gelatine capsule filled with cotton or gauze. The train of symptoms—lethargy and vomiting—dated from the time of operation, and was considered undoubted internal hydrocephalus. Frazier and Peet (7), using a slightly different method, observed the same phenomena in their animals, but the onset was noticeably slower. Neither of these authors specifically claim that their experiments prove that the fluid is formed by the choroid plexus, but it is easy for the reader to infer that the experiments make it more than probable that such is the case. In actual fact these experiments do not prove the point of origin of fluid beyond the fact that it may originate above the aqueduct of Sylvius; they simply confirmed the well-known facts of internal hydrocephalus. They do not prove the specific point of formation, for in the region under observation increased formation might result from activity of the choroid plexus, from stimulation of the ependyma cells lining the ventricles, from increased transudation from the capillaries or from the formation of intracranial lymph: any one or all of these factors may be involved. Further, the rate of formation may be perfectly normal, the whole pathology being merely decreased absorption.

The same objections hold for the experiments of Weed and Cushing (8), who in the title of their paper: "Studies on cerebrospinal fluid. The effect of pituitary extract upon its secretion (choroidorrhoe)" go on record as accepting as a fact the *secretion* of the fluid by the choroid plexus, and apply the term "choroidorrhoe" to the apparent but not necessarily real "increased secretory activity of the choroid."

These authors believe that the secretory rôle of the choroid in the formation of the fluid is proved by the work of Cappelleti (2), Petit and Girard (3) and others; and on the basis of secretion they explain their observations which are recorded in two places: *a*, Experiments described in general terms by Weed (9), in which the aqueduct was catheterized after which a few drops of fluid escaped. This was followed by a "flow for from three to four hours, the rate of escape from the catheter being gradually slowed. The final cessation of flow is apparently due to exhaustion of the choroid plexus under experimental conditions." *b*, Experiments reported by Weed and Cushing (8) on animals in which the fluid was allowed to escape from the *cisterna magna* and from the third ventricle. In some of the latter the aqueduct was catheterized, in others a needle was inserted into the third ventricle through the *corpus callosum*. Neither of these experiments proves the seat of origin of the fluid to be the choroid for any of the factors mentioned above may be concerned here as well. They do not eliminate positively in all their experiments the possibility of the flow being due entirely to preformed fluid, or to fluid formed under decreased pressure during the experiment. The details of the criticism will be taken up later. The observation of Cushing in man that ligation of the choroid is followed by a cessation of the secretion is to the point. Unfortunately the author does not state whether the immediate cessation was a stopping of the "sweating" process observed at the time of operation or whether the ligation was followed by a permanent cessation of symptoms due to excessive formation. We are inclined to believe that no excessive formation was present in the case cited by the author named, so the former must have been meant, for he says: "On one or two occasions, I have had the opportunity in man to observe the main plexus at the bottom of a large porencephalic cavity, emptied of its contents, and have seen the fluid exuding from the surface of the structure. In one . . . . the plexus was removed, and in another the entering blood vessels were ligated with immediate cessation of the secretion." He evidently considers this a direct observation of the *normal* function of the plexus in secreting the fluid. Weed observed sweating of the pia-arachnoid but considers it *pathological*, primarily due to alteration of the pressure on the membrane after removal of the calvarium. However, this observation was made long before that recorded by Weed, for Spina (10) reports: If adrenal extract is injected intravenously into a curarized dog, the brain which has been laid bare for direct observation becomes hyperemic, swells

and becomes more wet; or,—a fact upon which special emphasis must be placed—drops of fluid appear upon the surface during the time the brain is enlarging. Thus it becomes evident that the appearance of drops of fluid upon the appendages of the brain is not confined to one structure, the choroid, for it is seen over the whole surface; and thus it is impossible to decide from direct observation which one of these *normally* gives rise to the fluid. In the observations cited, those by Cushing were made under conditions practically identical with those by Weed; if one set was pathological, then the other must have been also. Neither does the effect of the ligation of the vessels entering the choroid plexus give convincing evidence on the subject, for such an operation would, by producing anemia, prevent either normal or pathological processes of new formation in almost any gland except the most resistant, and even in these activity would be possible only for a few minutes at most.

Experiments in dogs in which the choroid has been removed, should prove this point, but to our knowledge such experiments of a conclusive character, although attempted many times (24), never were performed with complete success, undoubtedly on account of the difficulty of removal of the plexus in the living animal. The reports in the literature are not complete enough, nor have enough experiments been performed successfully to draw definite conclusions as regard the function of the choroid, and its relation to fluid formation.

Finally, the experiments of Dixon and Halliburton (11), (12) may be interpreted as showing the specific action of the choroid in the formation of cerebrospinal fluid, for these authors claim to have observed increased formation of the fluid following the injection of extracts of the choroid plexus, homologous and heterologous in origin. The evidence offered on this point by these authors is not conclusive, because their results will be shown to be capable of an explanation on an entirely mechanical basis. These extracts produced marked mechanical changes in the vascular system, and these changes, not increased secretion in response to a specific hormone, may well have been the cause of the change in volume of the contents of the dural canal and hence of the fluid pressure, or the rate at which the fluid escaped from the needle. Further, the extracts of choroid plexus act upon other structures as well, having a rather marked lymphagogue action.

A consideration of the facts as stated shows clearly that the point of origin of the fluid, the structures concerned in its elaboration, and the nature of the process involved, are not known. Our own work in the

field does not bear on this point more than that of our predecessors. For that reason we say frankly that we do not know the point of origin nor the mechanism of formation of the cerebrospinal fluid. While far from being prejudiced against the secretory theory of the formation of the fluid, we do not believe that there is as yet any clear-cut evidence that the actual process of formation is secretory or that the fluid comes normally from the choroid plexus.

Critical review of the movements of the fluid

The second problem—the movements of the fluid in the canal—is the one usually studied when the problem of "the formation of the cerebrospinal fluid" is under consideration. But as has already been pointed out, the rate of outflow or the alterations in pressure may have absolutely no relation to the rate of new formation. The amount of fluid in the canal may remain constant, but owing to increased volume or pressure of blood in the skull, or the increased oscillations, the amount of fluid escaping or the pressure recorded by a manometer, may be markedly increased. The difficulties encountered in the study of this process are numerous: New formation and absorption may or may not be going on, both at unknown rates. If the method adopted requires the emptying of the dural canal, as so many do, some fluid will always be left behind, no one knows how much or how little. If a part or all of the fluid is emptied from the canal, the removal by reduction of pressure alters conditions within the system to such an extent that the mechanism of formation may change entirely, the normal being held in check and a new one instituted. The study of the cerebrospinal fluid formation is surrounded by the same difficulties encountered in the study of the formation of urine, if the experimenter had to work on an animal with a rigid abdomen, which could not be opened, with the bladder replaced by a rigid vessel of unknown size partly filled with unknown and varying amounts of fluid, some being newly formed, some being absorbed through the natural pathway, with the urethra the only avenue of approach. Moreover to increase the difficulty in the case of the fluid no natural avenue of approach exists, so an artificial one must be made, usually by the insertion of a needle at some convenient point into the canal.

Limiting the study to the behavior of the fluid rendered accessible by inserting a needle or cannula into the subarachnoid space or one of its communicating cavities, a review of the methods employed in

the study of the problem becomes necessary. These methods fall naturally into two classes and a number of modifications, each having some advantages over the other. In one case the attempt is made to determine the amount of fluid formed *directly*, by measuring the rate of outflow of fluid in drops; in the other, to arrive at the amount formed *indirectly* by measuring the alterations in the pressure of the fluid. As is evident from this first and simplest statement, the outflow method can record only those cases in which there is an increase in the fluid, and hence it is only as applicable as a maximum manometer would be to all the phenomena of blood pressures. The pressure method is adapted to measure both increases and decreases in the volume of fluid. Thus in our judgment the latter method is far preferable to the former or any of its modifications.

Outflow methods

1. Temporary fistulae. Temporary and permanent fistulae have been established. The first we noted to have used the fistula method was Magendie (13). To enumerate all those who have used this method, some employing the lumbar region and others the simpler expedient of inserting the needle into the canal through the occipito-atlantal ligament, would involve unnecessary repetition. This method, or some of its modifications, is the one most commonly used in the past. The slow dropping of fluid from the needle after the first gush has ceased has been considered the normal rate of formation, for it has been argued that a drop of fluid must have been formed within the canal, else the drop just lost would not have made its escape. The drops have been recorded electrically on a smoked drum, thus making a graphic record of the experiment.

Some of the sources of error in the outflow method are so obvious as to be self-evident, others are more subtle: The *first* is the objection to the alterations of pressure. Much of the fluid already present in the canal, and much of that possibly being formed during the course of the experiment, is drained out, thus reducing the pressure in the canal which is normally positive to, or almost to, zero—a change which in itself will probably produce changes in the rate of formation, in either a positive or a negative direction, with the former the more probable. For this reason it is more than likely that the enormous quantities of fluid reported by clinicians as draining from the ear or the nose, in cases of congenital defect or after compound fracture of

the skull, represent not the normal rate of formation but the surprising powers of the structures producing the fluid to regenerate it after loss. On the other hand, this fluid may not be of normal composition at all, but a transudate from the blood exuding in drops because of the abnormal differences between the pressure in the blood vessels and the pressure in the dural canal. A process of this kind can best be observed by injecting adrenalin intravenously after removal of the calvarium, so that the pia mater may be observed directly. In this experiment drops of water (fluid) appear on the pia and to this process the term "sweating" has been applied (10). Whether this is the normal mechanism working at a higher rate than normal, or an abnormal mechanism, has not been determined, but we believe the latter view to be the more probable one.

Some of the later investigators recognized the validity of this objection. Thus Weed and Cushing (8) attempted to avoid the reduction of the intradural pressure by substituting for the wide needle a narrow one or a catheter calibrated to deliver fluid under a pressure estimated to be equal to that normally existing in the canal. They limited the maximum pressure at all times to the resistance of the catheter or needle, even in the animals subjected to pituitrin injections in which it can be shown by other methods the fluid pressure may rise far above the normal. Hence their method does not do what they claim for it: "Pressures approximating the normal were maintained within the ventricles." For while the resistance offered by the catheter or the needle may be the normal at the *beginning* for the animal without injection, it ceases to be the normal with the injection, for this resistance does not increase as the pressure in the skull increases, as would be the case in the intact canal. Therefore, the outflow may show not new formation, but increased outflow of fluid displaced by the increased intracranial pressure, due to vascular changes. Since the vascular pressure changes and the pressure of the cerebrospinal fluid remains the same, being limited to the resistance of the needle, it follows that the differences in the pressure of the fluid in the vessels and the fluid in the subarachnoid space is greater by this method as well as by the other. These pressure differences are somewhat smaller than by the ordinary outflow method, but are in the same direction, hence the conditions necessary for filtration or for transudation exist but in a smaller degree in this method as well as in the older ones. (See fig. 6 in the following article).

A further objection is the fact that by the outflow method the pressure of fluid in the canal is limited artificially at all times to the pressure required to force fluid through the needle, instead of being higher or lower depending upon the vascular condition of the skull. For this reason under the influence of hemodynamic drugs or under physiological manipulation, the differences between arterial and venous pressures on the one hand and fluid pressure on the other become abnormally great—a condition which does not arise under some of the other methods employed. This error is only a variation of the error due to reducing the pressure by emptying the canal.

The *second* objection to the outflow method is the inability of any worker to empty the canal completely. A consideration alone of the complicated system of passages and reservoirs is sufficient to bear out this statement. There is sure to be blocking of a part of the fluid at some strait in the system either within or without the central nervous system. Then, later, when the experiment is under way, and the cord and the medulla move with each respiration and each heart beat—uniform movement of the anesthetic is properly adjusted—this preformed fluid flows from a higher to a lower level from gravity, or from a cavity under higher pressure to the fourth ventricle where the pressure is limited as a maximum to the pressure required to force liquid through the needle. Then it escapes gradually and steadily to the outside, simulating a "normal rate" of secretion. A uniform rate of escape, it is true, but this is not necessarily a measure of the rate of formation, for it may be only a measure of the rate of escape of preformed fluid, or the rate at which it may be formed if its free escape is permitted. This outflow of preformed fluid, we believe, is the so-called "normal rate of formation" recorded by many authors. This flow is said not to persist after the fifth hour, even in an animal as large as a goat (11), where the blood pressure is still fairly high at the end of the experiment, a fact which makes our explanation that the "normal rate of formation" represents the leakage of preformed fluid all the more probable.

Numerous expedients have been adopted to avoid this error. The best was the one adopted by Dixon and Halliburton who abandoned the outflow for the manometer method. Weed and Cushing attempted to eliminate it by showing that in some experiments after ventricular cathetherization the total amount of fluid collected was greater than that normally found in the ventricles. This expedient is hardly satisfactory because the amount found in the ventricles varies within such wide limits. In our opinion 3 cc. is a large but not abnormal amount

of fluid, for we have several times collected as much from the ventricles of cats in some work on immunity, where normal animals were used. The expedient of transcallosal puncture did not avoid this error for when they enter the third ventricle by the transcallosal route, they leave the aqueduct of Sylvius open; therefore, as the pressure in the third ventricle is lowered by drainage all the fluid in the fourth ventricle and in the subarachnoid space can be drawn upon to make good the deficit. While it is believed the direction of the flow of fluid is normally from the third ventricle into the fourth through the aqueduct, there is no reason for thinking that under the conditions of this experiment the movement of fluid might not be in the opposite direction, also. This is borne out by experiment: If a saline solution of methylene blue is injected in small amount—1 cc.—into the fourth ventricle of an animal with a trocar in the third ventricle according to the method of Weed and Cushing, the dye appears at once in the fluid from the third ventricle. Low pressure was used in the injection. This shows that the fluid can pass from the fourth to the third ventricle, and that in the experiments described, except in those in which catheterization of the ventricle was practised, the fluid secured from the third ventricle was subject to the same influences as the fluid secured from the *cisterna magna* by the other method. And even in those experiments in which the third ventricle was catheterized the fluid is subject to the alteration of pressures and the data to the error pointed out for the outflow method in general. And in our opinion if time enough is given the subdural space will be drained by transcallosal puncture as well as by a puncture into the fourth ventricle. Closely related to this objection is the inability to differentiate between newly formed and preformed fluid.

Nearly all our recent predecessors (8), (11), (14), have depended upon the recession of fluid into the tube to differentiate between preformed and newly formed fluid. They believe that if there has been increased vascularity of the brain there will be an acceleration of the rate of flow (8, p. 101):

> Then with subsequent lowering of the congestion on the arterial or venous side, as the case may be, the fluid will be observed to recede into the cannula to compensate for the decreasing vascularity. On the other hand, if fluid is actually being secreted no such recession is observed, and though the rate may be slowed fluid continues to appear in spite of the relatively devascularized brain.

We must point out that this method of differentiation need not give such good results as might at first glance be expected of it. It is well known that both brain and cord, because of their large water content, are practically incompressible; because of its bony structure the skull and neural canal are nearly undilatable to pressure except at the membranes covering the foramina between the vertebrae. To the same degree that the brain is incompressible and the skull undilatable by pressure are they lacking in elastic recoil when the pressure is removed. So when the vascular pressure falls or becomes stationary after the effects of the drug have worn off, no very efficient elastic rebound in the intracranial structures can occur, and hence no great negative pressure can be developed. For this reason the strong sucking back of fluid against the resistance offered by the catheter upon which they depended to differentiate the mechanical from the secretory need not occur at all. Further, the limitation of the intracranial pressure to the normal or less as a maximum, as is done in the outflow method, works against the development of a strong negative pressure. Only by exerting powerful pressure in compressing an object can that object respond by strong rebound when the pressure is removed. This constitutes a second reason why strong sucking back need not be a constant phenomenon in employing this method for the study of the cerebrospinal fluid. For the same reason it does not follow necessarily that in all those cases in which no recession in the tube was observed, new formation had occurred.

A *third* objection to the outflow method is the inability to judge the effect on the fluid of vascular change and readjustment. Alterations in the arterial and venous pressures in the skull exert more influence upon the fluid in the canal than a similar change in pressure in the blood vessels would upon fluid in any other part of the body. The brain is incompressible, the bony calvarium prevents any expansion, and thus any rise in arterial or in venous pressure exerts a marked effect upon the fluid pressure. The fluid then moves outward through the needle because of low pressure outside and high pressure within. Further, the cerebral arteries behave differently from other arteries of the body apparently becoming widened instead of narrowed under conditions of a general rise in blood pressure such as follow the administration of the drug adrenalin. At least the pressure in the subarachnoid space is markedly increased instead of decreased as would be expected if the cerebral vessels responded in a manner similar to blood vessels elsewhere. (See fig. 11). The explanation usually made, of

course, is that there are no vasomotor nerves to the vessels of the brain, or if such exist, they are so feeble in their action that the vessels are passively dilated under the influence of high general blood pressure in spite of the constriction attempted. The existence of vasomotor nerves to the brain has never been proved although many physiologists have carried out experiments in which their existence was suggested. Further, anatomists have described in the walls of the cerebral vessels, structures which in other parts of the body are considered vasomotor nerve endings. Under the conditions described, anything altering the arterial or venous pressure or the respiratory rate and depth will alter the rate of escape of the fluid. So long as the pressure is higher than normal, the fluid in the canal is under greater pressure, and some of it, which normally would remain in the canal, is forced out and drops off, a process which does *not necessarily cease when the pressure begins to fall,* but which may continue so long as the pressure is higher than it was in the beginning of the action. This persistence of the action is one of the factors which has led to confusion, but the explanation is easy if the true condition in the canal is recognized. This undoubtedly explains some of the flow of fluid persisting after arterial pressure has fallen. When the vascular normal is reëstablished, the fluid which has dropped off is no longer available, and in some instances air is drawn into the cavity. This fact has been observed by nearly all the recent workers in the field. However, apparently they did not recognize that so far as that animal is concerned further observations are useless, for no one knows how much of the intracranial space is taken up by air, how much by fluid. Besides, with the outflow method as described the observer has no way of studying the effect of vascular readjustment upon the fluid for when the fluid has retreated out of sight into the tube, it does not reappear for a long time unless another hemodynamic drug is given. This mechanical forcing out of the fluid has been recorded as "secretion" and is the cause of the "increased formation" of fluid under the influence of hemodynamic drugs, to which class most of the drugs and extracts described as having a stimulating effect upon the formation of cerebrospinal fluid belong.

Thus the method is not applicable to a study of the fluid in those conditions in which a recession is to be expected. It is only as applicable to this problem as a maximum manometer is to the study of all the phenomena of blood pressure. When this method is used any rise in the arterial or venous pressure—produced by the pressor nature of the substance injected—raises the blood pressure in the skull sufficiently to force the fluid out through the catheter.

Frazier and Peet attempted to avoid this error by permitting the fluid to flow into a graduated tube adjusted level. In addition to having the point of outflow the lowest point in the system this method practically limits the observation to outflow only, for the very obvious reason that water never flows up hill, unless under the influence of some pressure. In an animal placed in the position they describe the regular pulsations to be observed in the brain and cord permit the fluid present to flow down the inclined planes offered by the cord and the meninges in one direction and by the brain in the other, and escape into the tube. This process is favored by a pressor effect upon the arterial and venous blood pressures, and by increased respiratory movements. As the effect of the drug or of the manipulation which induced the change in blood pressure wears off, and readjustment takes place within the skull, and the pressure having been limited throughout to the resistance of the needle as a maximum and thus low, the inelasticity of the structures under pressure prevents the development of enough negative pressure to suck the contents of the tube back, if there is much resistance from gravity, as would surely be the case in the experiments described. Since their records are in one-hundredths of a cubic centimeter, their tube must have been of fine bore, so to the force of gravity which has to be overcome must be added the resistance of the tube and capillarity. In spite of the marked disadvantage to which they subjected the fluid in their experiments, they observed return of the fluid in many cases. If a strong negative pressure could develop the increased formation might be due to "*edema ex vacuo.*"

Fourth, it is conceivable that in an animal in which the outflow method is used, the resistance offered by the cerebrospinal fluid in passing through the needle outward from the skull is less than that offered by the blood in passing by natural channels to the heart. When this occurs the amount of blood accumulating in the sinuses would increase at the expense of the cerebrospinal fluid. The accumulation of blood would then displace an equal amount of fluid, thus setting up a pseudo-secretion without a rise either in cerebrospinal or in venous pressure.

Fifth, one further possibility must be considered: Under normal conditions found in the skull the transfer of fluid from the extracerebral part of the cerebral cavity to the cerebellar cavity and the fourth ventricle is more or less difficult, because of the fact that the way is almost completely blocked, mainly by the cerebral peduncles and the *tentorium cerebelli.* This was pointed out by Hill (18, p. 19), and we

would add that what space remains must be completely blocked by the circle of Willis and the sinuses at the base of the brain. Since this is true, it is easy to see that a rise in venous pressure will displace the fluid around the medulla and cerebellum readily with the outflow already described, but at the same time will render the passage of fluid from the cerebral cavity more difficult. However, Dixon and Halliburton have already shown that depressor substances like amyl nitrite increase the outflow of fluid. We will show that this is true, not only when venous pressure rises, but when it falls (fig. 36). Therefore, there must be furnished an adequate explanation of the mechanism of increased outflow with both arterial and venous pressures falling. We believe the correct explanation to be as follows: With a considerable amount of fluid present in the cerebral cavity, a fall in both arterial and venous pressure causes a shrinkage of the cranial contents, particularly of the sinuses around the base of the brain. This shrinkage increases the ease with which fluid passes this strait, and permits the contents of the extracerebral part of the cerebral cavity at a higher level than the medulla to flow down into the vicinity of the fourth ventricle and thus drain out through the needle. This explains many of the occasionally observed but by no means constant increased outflows with reduced arterial and venous pressures. If it so happens that the cerebral cavity is practically empty, then the shrinkage of these structures lets the fluid escape from the fourth ventricle into the cerebral cavity instead of through the needle with the result that fluid outflow decreases, stops altogether, or the fluid may recede in the needle. Both increased and decreased outflow with falling arterial and venous pressures have been observed. (See fig. 36).

The position adopted for their animals by Frazier and Peet (7, p. 275), "by placing the subject on an inclined plane head down so that the occipito-atlantal ligament was under the most dependent portion" would give the maximum effect so far as the outflow of fluid is concerned when substances reducing both arterial and venous pressures are injected. Their responses to tissue extracts were much more marked than our own using the outflow method.

Sixth, if the outflow method of recording the fluid is used it is absolutely necessary that respiratory tracings be taken. Increasing the respiratory movements increases the oscillation of fluid in the canal. Thus any drug or physiological manipulation which produces altered respiratory rhythm, irrespective of whether it alters blood pressure or not will have an influence upon the rate of flow from the needle. The

reason for this increased outflow is apparent. When the needle is inserted the canal is drained until the surface of the fluid in the canal is level with the lumen of the trocar. Then any increase in the oscillations of fluid in the canal such as would be produced by greater respiratory efforts will increase the leakage through the needle, in exactly the same way that waves produced on the surface of a tank would increase the leakage through a hole in the side at the level of the surface of the water. In addition the rate at which fluid will be released from the various cavities at higher levels or under greater pressure will be increased by the increased movements of the nervous system. On the other hand we have seen cases in which increasing the respiratory movement decreased the outflow of fluid, an observation to be explained on physical grounds only by the supposition that the fluid flows into some lower lying cavity, or into one under less pressure. (See fig. 17).

From this discussion it is clear that the outflow method for the study of the rate of formation of the cerebrospinal fluid is unsatisfactory.

To summarize the objections to the outflow method: The reduction of pressure within the dural canal, the inability completely to empty the canal, the limitation of the pressure to the resistance of the needle as a maximum, the inability of studying the behavior of the fluid during vascular readjustment by furnishing fluid to the canal while the adjustment is occurring, the inability to control changes due to alterations in respiratory rate and strength, all these make this method unsuitable for the problem. Dixon and Halliburton (11) used it in their early work, but discarded it later. We had already discarded if before the appearance of their papers. Using this method we secured graphs identical with theirs, but since so many factors were left uncontrolled, we discarded the experiments as worthless. Many recent writers have used this method without any recognition of its limitations. We believe that to prove normal new formation by the outflow method, it must first be granted that complete emptying of the canal is possible, and that the reduction of the pressure does not alter the processes of formation either as regards rate or mechanism. In addition to granting these two points—which no careful worker can grant—it must be shown that the increase is independent of vascular changes within the skull or respiratory changes. An attempt to "standardize" the animal by estimating by experiment the influence of arterial, venous and respiratory changes leads into dangerous territory, because of the wide variations in different animals and in the

same animal from time to time, partly because of differences in the amount of fluid in the canal, partly because of the differences in reaction after the prolonged action of an anesthetic. This will be shown clearly in the experiments, later. We believe that most of what is observed in the experiments where the outflow method is used is the escape of preformed fluid. In some of the experiments it is squeezed out at an increased rate by a rise in the arterial or the venous pressure or both, and by an alteration in the respiratory rate. To this fluid is added, perhaps, some newly formed fluid arising under conditions of reduced pressure which exist in the canal because of the abnormal differences in pressure between the blood in the vessels and the fluid. This newly formed fluid must of necessity be of uncertain amount, the method gives no way of determining it or of distinguishing it from the rest of the fluid, and further it may be formed by a mechanism entirely abnormal, so that even if it were measured accurately, it would give no clue regarding the normal rate or the normal mechanism of the formation of the cerebrosphinal fluid.

2. Permanent fistulae. Permanent fistulae were introduced first by Cavazanni (15) for the observation of the formation of the fluid under the condition of constant loss, and may be valuable for the study of the variations in the chemistry of the fluid if the infected animals are rejected. This method can give no data regarding the mechanism and rate of formation of the fluid over periods of long duration. The objections mentioned against the temporary fistula are valid here, and in addition the voluntary movements of the animal without an anesthetic would make the observation of slight variations of the formation of no significance whatever.

Manometric methods

The manometric method was introduced by Leyden (16) with excellent results. Both increased and decreased pressures are recorded, and any increased pressure of the fluid persisting for an appreciable time and independent of changes in the arterial and venous pressures in the skull, is interpreted as indirect evidence of new formation of the fluid. Dixon and Halliburton (12) used this method in their later work. The advantages to be pointed out are the following: This method avoids the error of incomplete emptying of the canal for the fluid is all retained within. It avoids the error due to the reduction of the pressure from partial drainage of the fluid from the canal. It

sets no maximum pressure within the canal, the pressure increases or decreases as in the intact animal. Only enough fluid need be removed to fill the manometer tube to the required height. For this reason it avoids the error due to new formation from abnormal differences between intravascular and intracranial pressures, when the pressure in the arteries and veins becomes too much higher than the fluid pressure. Thus the pressure of the cerebrospinal fluid varies within the normal limits of the intact animal and does not remain constant throughout the experiment as in the cases studied by the outflow method. If the process studied involves a fall in the pressure in the blood vessels shown ordinarily by the recession of fluid in the tube, the manometer records this change as well as a rise in pressure, thus it is adapted to study both the pressor and the depressor phase.

However, when using the manometer method for studying the behavior of the fluid, certain precautions must be observed: A failure to do this has led to some surprising errors on the part of some observers. The needle connecting the canal with the manometer must be wide, otherwise there will be considerable delay in the rise of pressure in the cerebrospinal fluid manometer in response to changes in the venous and arterial pressures. This shows itself on the tracing by a rise in cerebrospinal fluid pressure which continues to become greater after the venous and arterial pressures begin to fall. When such a phenomenon occurs, naturally it need not be interpreted as meaning that the rise is not due to alteration in the arterial or venous pressure, because it is not synchronous with it, for it *is* due to those alterations. The significance which must be read into it is that there was an obstruction somewhere and the maximum ultimately recorded by the cerebrospinal fluid manometer is not the true maximum, but a pressure somewhat lower; lower by the amount of arterial or venous fall which occurred between the arterial and venous maximum and the cerebrospinal fluid maximum. This is of importance only in those cases where the pressure changes are very rapid in both directions as, for example, after adrenalin. Not all the trouble lies in the needle, a part may lie in the aqueduct of Sylvius and in other straits in the canal. Of course these latter errors cannot be avoided, and hence too much significance should not be placed upon the observation that changes in the fluid pressure are not absolutely synchronous with, or in the same direction as changes in arterial and venous pressures. We have observed arterial and venous pressures falling with the fluid pressure still rising, but such a rise was the result of the increased venous pressure, and stops short of

the height which would have been reached had the venous pressure become stationary when the high point was reached.

Great care must be exercised in the selection of the manometer tube in the case of the cerebrospinal fluid. If the bore is too small it offers too much resistance to the movements of the fluid and the influence of capillarity upon the level sought by the fluid is too great. If the bore is too large, the volume drained from the canal is too great, and the manometer shows a pressure which is not the pressure of the fluid in the intact animal, but the pressure of the fluid in the intact animal minus the amount of fluid withdrawn in filling the manometer tube. On the other hand if the manipulation involves a fall in pressure, and the bore of the manometer is large, the pressure recorded will not be the pressure of a normal animal under similar conditions, but will be the pressure of the normal animal with the canal overfilled by the volume of fluid equal to that which flowed in from the manometer. The importance of this point will be brought out and substantiated more fully. The use of a tambour to record manometric pressure is unsatisfactory. Most tambours leak, slowly it is true if proper precautions are observed, but rapidly enough, where delicate rubber is used, as in this case, to make standardization of little value. This is especially true if the pressure changes are of long duration either in positive or negative direction. The lever of the tambour traces the arc of a circle, not a vertical line, and hence the true time relations are in doubt. This is especially true if one tambour is set to write in one direction, the other in the other. Marked examples of this type of result are seen in graphs published in some of the latest work (12).

We finally come to the most fundamental objection to the use of the manometer to record variations in the cerebrospinal fluid pressure. These are two in number: the pressure conditions are such as to facilitate the absorption of the cerebrospinal fluid along the natural channels, hence the fall in the pressure of the cerebrospinal fluid observed in many cases may be due in part to vascular readjustment, in part to absorption of fluid along the natural channels, or either may be active independently of the other. In either case it is impossible to estimate the part played by each factor, if absorption actually enters into the problem, as must be the case if formation and absorption are as rapid as the clinical evidence given indicates. There is however good evidence that the rôle played by absorption in this readjustment is a minor one, for as will be shown later ligation of the jugular veins—along which it is agreed that most absorption takes place—does not

alter essentially the behavior of an animal in response to the injection of such drugs as pilocarpine. Further, the fall in the cerebrospinal pressure is synchronous with the fall in venous pressure and arterial pressure. The second plausible objection to the manometer method is the possibility that the cerebrospinal fluid is secreted under low pressures only, and hence might cease to be secreted at a pressure so low that it is impossible to indicate it by means of the manometer. This objection is not valid; it is evident from certain clinical cases that cerebrospinal fluid is secreted, or at least exists at high pressures; besides the manometer merely records the pressure and its physiological variations, and produces no new pressure of itself. Hence it cannot be blamed for raising the pressure above the limit at which fluid can be formed.

II. EXPERIMENTAL METHODS EMPLOYED IN THE STUDY OF THE FLUID

It is our intention to describe in detail the methods used in our study of the cerebrospinal fluid.

Anesthesia: The effects of the alterations in the anesthesia are such as to make a constant degree necessary. We found constant slow intratracheal insufflation admirably adapted to this purpose. A constant degree of anesthesia is still more easily obtained if a dose of morphine is given preliminary to the anesthetic, but we avoided the use of the latter drug because of the tendency of an animal under its influence to show wide variations in the respiratory rhythm, with periods of apnea and dyspnea alternating, variations reflected upon the fluid by the production of undesirably wide fluctuations with each respiration, and alterations in the general blood pressure levels, with the periodic respiration. In our later work ether alone was given by inhalation, and proved perfectly satisfactory, when we employed a special valve prepared to give a uniform mixture of air and ether.

Arterial pressure: The arterial pressure was recorded by the mercury manometer from the left carotid or the femoral, in nearly all cases from the former. In some animals the pressure was taken in the circle of Willis according to the method of Hürthle (19). This pressure is not necessary in all cases because it usually follows faithfully the arterial pressure in the carotid, except where the cerebral arteries are ligated or in the cases of some of the drugs. The former requires no discussion, the latter will be taken up in detail later. For anything like accurate results in the circle of Willis, large dogs with

a wide internal carotid are necessary, and even in these the results are not always satisfactory. However, the method shows the changes in a general, even if not in an absolutely accurate way.

Venous pressure: It became evident early in this work that in these experiments the measurement of the arterial pressure alone is not enough to control alterations in the pressure of the cerebrospinal fluid due to mechanical factors. For this reason, especially for lack of the venous pressure in the head, some of the recent work is of little value in determining the mechanism of fluid formation. (Frazier and Peet (7), (14), and Weed and Cushing (8), (9)). Some of the conclusions are correct but that is true simply because venous pressures in the cases under observation follow the arterial pressures directly, and their experiments did not prove the facts in the case. The venous pressure must be taken from the head, for the pressure in the heart or in the superior vena cava has little or no relation to the pressure in the skull. (See table 1 and fig. 1).

In our experiments if we failed to establish venous pressure the animal was discarded as useless. We use a venous pressure method copied in part from Burton Opitz (17), in part from Hill (18), and modified to suit our own needs: a brass tube 1 cm. long and 4 mm. in diameter provided with a reservoir of about 40 cc. capacity, filled with a solution of sodium carbonate with a specific gravity of 1.088 is screwed into a drill hole made into the torcular herophili through the external occipital protuberance. The tube and reservoir are connected with a manometer filled with the same carbonate solution. Before opening the clamp and permitting the fluid in the bulb to communicate with that in the manometer, the pressure is raised in the latter to a point a few centimeters higher than that usually found in the sinus, so as to force a small amount of the solution into the sinus, and thus avoid the clotting in the system from the accumulation of blood in the short tube between the sinus and the reservoir. If this precaution is observed venous pressure can be studied for hours without enough clotting in the apparatus to make the error appreciable. A *post mortem* must be made in every case to rule out clotting, for with carbonate solutions the whole sinus system may be filled with a fine membranous clot which markedly interferes with the venous outflow, and it is common to find in many experiments venous and fluid pressures rising slowly but steadily throughout the period of observation. The mechanism recording on the drum includes a three or four unit signal magnet. An observer watches the level of the sodium carbonate in the manometer

and records the variations in pressure by closing the key in one magnet circuit, once if the level rises past a centimeter mark on the scale, twice if it falls below the mark. In our earlier experiments the manom-

TABLE 1

This table shows the relation between arterial pressure, venous pressure in the torcula, and venous pressure in the stump of the axillary vein, where the latter joins the jugulars

	ARTERIAL			GENERAL VENOUS			TORCULAR VENOUS		
	B.	D.	A.	B.	D.	A.	B.	D.	A.
Pilocarpine	114	86 140	104	85	155	100	90	130	110
	122	100 160	104	15	30	15	105	269	105
	78	94	70	−25	−30	−25	40	85	40
	116	92 146	110	−5	70	0	10	19	10
	112	70 170	90	5	84	5	225	315	220
	140	112 160	130	1	1	1	5	240	100
	130	30 140	110	1	1	1	235	300	240
Nicotine	80	170	32	3	3	3	30	38	30
	92	150	98	0	−1	1	20	26	22
Adrenalin	100	210	92	0	0	0	12	19	12
	64	240	58	−35	−35	−35	25	285	95
	60	246	78	−1	−8	−1	5	210	10
	134	278	118	1	−8	1	11	39	12
	80	168	80	2	5	2	7	18	14
	80	186	74	3	6	2	12	27	12

B = Before the action; D = During the action; A = After the action of the drug. Where two figures are given, these figures represent the minimum and maximum.

eter was connected with a tambour covered with the thinnest rubber obtainable, in addition to the record described. In most of our later experiments the tambour was discarded because errors from leak-

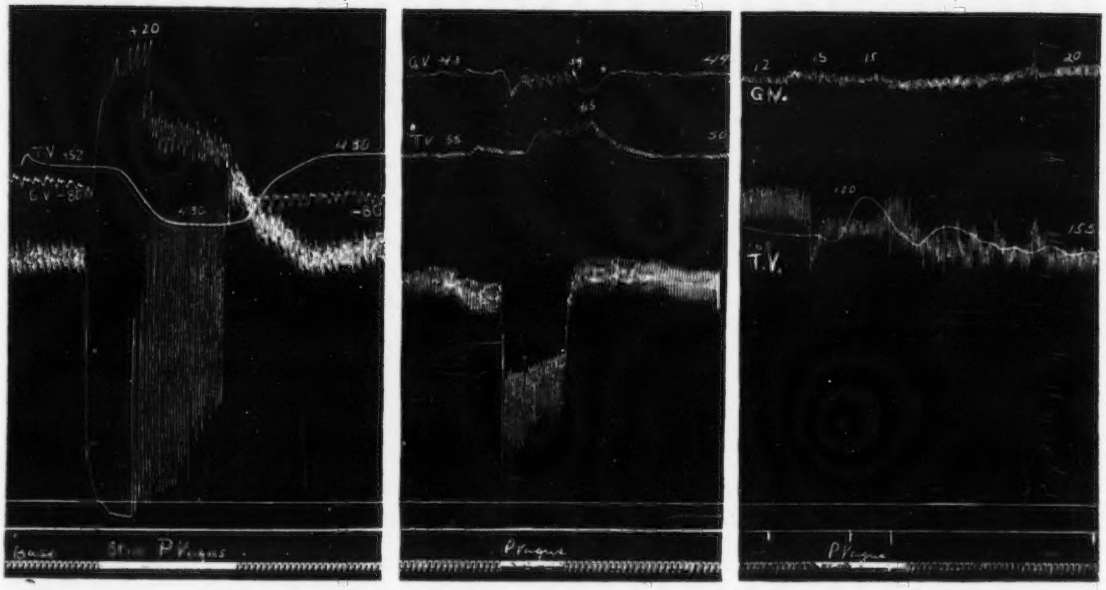

Fig. 1. These tracings show the different reactions of general and cerebral venous pressures in different animals in response to the stimulation of the peripheral vagus. A comparison of torcular, *T. V.*, and general, *G. V.*, pressures shows marked differences in behavior and emphasizes the importance of the measurement of venous pressure in the skull, not in the great veins of the body, when conclusions are to be drawn regarding the cause of pressure changes in the head.

age made the record untrustworthy, time relations were altered, and in addition we found it advantageous to use a small manometer tube, the variations of which were too small to give a suitable tracing. In no case did we depend upon the tambour to determine the actual variations in pressure, since this can be read directly from the magnet record. In addition from time to time—e.g., when we knew by experience that the maximum or minimum point had been reached, or at regular intervals—simultaneous venous and fluid pressure readings were made, and recorded directly on the tracings after the paper was removed from the drum. General venous pressure was recorded in some cases from the axillary vein, where it joins the jugulars. We avoided the right auricle because of difficulties from clotting, but mainly because we did not want to interfere with venous outflow from the brain by cutting off one of the jugulars, or by occluding even in part the superior vena cava.

Cerebrospinal fluid pressure: In our determinations of the behavior of the cerebrospinal fluid under various experimental conditions we employed two methods: The first was a simple one we devised, only to find later that it was essentially the method used by Spina (10). The animal is placed on its side on a level table. The trocar is inserted into the *cisterna magna*, and after the obturator is removed the trocar is connected at once by means of a T-tube to a heavy piece of glass tubing 1 m. long with a uniform internal bore of 1 mm. This glass tube is fastened on a meter stick with centimeter markings, which furnishes the scale. The tube is then adjusted on stands so that the lower end attached to the needle is at exactly the level of the point of puncture of the occipito-atlantal ligament; the upper free end is adjusted to the level of the upper border of the cerebral hemispheres. Thus there is provided a water gauge showing pressure variations of the liquid in the dural canal. The fluid escaping while the connection is being made is collected and replaced into the system through the T-tube. This step is important for during the early part of our work this point was not appreciated and in many cases the early tracings were marked "animal refractory to drugs." Later it was found that a refractory animal became a susceptible one if the canal was filled with fluid (see table 15). As in the case of venous pressure, an observer watches the column of fluid oscillating in the tube and records the variations in the same way by closing a key in the proper magnet circuit. While this method requires the constant attention of one person, it is accurate because any blocking of the passage to the canal is noted at once by the disappearance of the oscillations. This method does not reduce the pressure by drain-

ing away fluid, complete drainage of the preformed fluid is not required nor attempted. There is no resistance to backflow of fluid produced by an artificial resistance as in the Weed-Cushing method. No maximal limit is imposed during the experiment; instead the pressures are maintained absolutely normal, the fluid is free to flow outward or inward depending upon whether the pressure within the skull is increasing or decreasing.

The only real objections to be advanced are the ones already pointed out against the manometer method: The fluid is under normal pressure, thus there may be absorption along natural channels; the pressures may be such as to inhibit the normal mechanism. However, it will be shown later that neither of the objections is valid.

While it would seem reasonable that the method described for recording variations in the cerebrospinal fluid would be adapted to the purpose of this research, it was necessary to determine the accuracy. To do this, experiments in which simple mechanical factors are known to be the only ones involved were undertaken. The most direct test imaginable is the direct injection of fluid into the dural canal. With the tube in place and connected in the manner described, numerous experiments were carried out. There were considerable variations between different animals but results in the same animal were uniform. Thus in one experiment the introduction of 4 cc. of warm 0.9 per cent sodium chloride solution changed the position of the fluid from 20 to 80. The withdrawal of 4 cc. brought the level of fluid again to 20. Repetition of this experiment numerous times showed that the error was less than 1 cm. on the scale, or in volume less than 0.031 cc. Of the 4 cc. increase in fluid 1.86 cc. appeared in the tube. In this case the needle through which the fluid was injected was 1 cm. from the trocar connected with the gauge. Injection of fluid in other parts of the canal produced less accurate results unless the injection was made into the third ventricle through the corpus callosum. In the latter case the results were almost as accurate as in the case of injection into the *cisterna magna*. Tests made with the manometer were equally satisfactory.

The second method employed was the manometer method already discussed. Our manometer had a bore of 1 mm., thus the question of draining the cavity if the fluid pressure is rising, or of overfilling it if the pressure is falling cannot enter to any degree. We at first used it as a check on the tube method described, but later we used it in most of the experiments because of the advantage that this method enables us to draw direct comparisons between fluid and venous pressures.

The medium used in the manometer was a sodium chloride solution with a specific gravity of 1.088 so as to make it directly comparable to the venous pressure. Sodium carbonate solution could not be used because of its toxicity if introduced intra-durally. Variations in the fluid pressure in this method were recorded in the same way as described for venous pressure.

Before entering upon the details of the experimental work, we wish once more to emphasize the importance of recording arterial, venous and cerebrospinal fluid pressuress continuously and simultaneously in every experiment. In some experiments the pressure in the circle of Willis is also essential. The continuous and simultaneous record is of the greatest importance, because of the unique conditions existing within the skull where is found the brain, incompressible to ordinary pressure, surrounded by the undilatable skull, and separated from it by the membranes, blood vessels and the cerebrospinal fluid. Any change of either venous or arterial pressure must be followed either by variations in pressure in or by variations in the amount of the cerebrospinal fluid. Hence in order to control properly the mechanical factors, both arterial and venous pressures must be measured, and the venous pressure because of its variability and because of its great direct influence upon the pressure is relatively, so far as the cerebrospinal fluid pressure is concerned, much more important than the arterial. The cerebrospinal fluid pressure is the sum of the influence of the arterial and venous pressures, as we will be able to prove later in the paper, so if both pressures rise the fluid will flow out in the tube, or will rise in the manometer; if both fall the fluid recedes in the tube or falls in the manometer. If one rises and the other falls—a situation which does occur under experinental conditions, actual measurement, not theory, will determine whether the cerebrospinal fluid pressure will rise or fall. From this statement of the situation the importance of these measurements becomes clear. We would not have had to dwell upon this point if the recent workers had read more carefully the excellent monograph by Hill on "The cerebral circulation." Because of additional data we ascribed more importance than Hill does to the direct influence of arterial pressure upon the cerebrospinal fluid pressure.

III. THE MECHANICAL FACTORS INFLUENCING THE CEREBROSPINAL FLUID

Introduction

A careful experimental study of the mechanical factors is imperative to establish the necessary controls for the work on the drugs and the tissue extracts, as well as to obtain a definite, concrete idea of the factors of error in the method employed. Provided by simple experiments with the controls and the factor of error for which we must allow, we will then be in a position to interpret the mechanism of action in the more complicated experiments. If a drug or a tissue extract gives a result which can be explained rationally on a mechanical basis, we are not justified in assuming that any other factor is at work. Only after the effect of a drug on the fluid cannot be explained on a mechanical basis, and not until then, is there any reason for ascribing to the substance a stimulating or depressing effect upon the mechanism generating the fluid.

In this section we intend to study the conditions of pressure that are found to exist in the normal animal, the various changes undergone by these pressures during long experiments under ether, and the mechanical forces which may influence the behavior of the cerebrospinal fluid. Of the latter the following are the more important: cerebral venous pressure, arterial pressure, respiration, the volume and pressure of the fluid in the skull, and the action of the vagus. Some of these clearly will have a direct, others only an indirect effect upon the fluid and its movements. No experiments by pressure methods upon the action of drugs and of tissue extracts in augmenting or inhibiting the formation of the cerebrospinal fluid can rest upon a satisfactory basis unless the natural relations of arterial, venous and fluid pressure are accurately known. It is also necessary to know what effect increasing or decreasing each of these pressures one or more at a time has on the others. Unless these facts are known it will be impossible to differentiate cause from effect. But when these facts are known, then it will be possible at least in part, in other and more complicated experiments to determine to what degree the purely mechanical changes of the arterial and venous pressure will account for the changes in the fluid pressure. In a case where the arterial pressure remains constant and both venous and fluid pressures rise, it is not possible without experiment to tell whether the pressure in the former rises because of the rise in the latter or *vice versa*, or whether they rise simultaneously but independently. If, however, experiment shows that raising the venous pressure raises the fluid pressure, but

raising the fluid pressure moderately does not raise the venous pressure, then we are justified in concluding that venous pressure influences the fluid pressure, but the fluid pressure does not influence the venous pressure.

At the beginning of the work it was hoped that in any one dog a certain change in the pressure in the arterial or the venous blood would always produce some certain change in the fluid pressure. Then, if the fluid pressure rose or fell more than was to be expected from the change in the vascular condition, it would be safe to assume increased formation or increased absorption. Unfortunately, these hopes were not realized. The amount of the influence varies widely in the same animal from time to time as will be shown conclusively later in the paper. For this reason the attempts to "standardize" a dog were abandoned after a few trials. Attempts to do this in the past have led to erroneous conclusions. If the reader will keep this in mind he will not be surprised in the apparent discrepancies in some of the experiments to be listed in our tables later.

1. The normal levels of venous, arterial and cerebrospinal fluid pressures

Having accepted the view that the best method of determining variations in the amount of fluid is the indirect one, by studying the pressure of the fluid in the canal, it is clear that a large number of measurements of normal pressures must be undertaken in order to obtain some idea of the limits of variation. This was done, and with the fluid pressure were made simultaneous measurements of arterial and venous pressures.

Literature: That the fluid is under positive pressure is a fact long well known. Leyden (16), probably the first to make measurements at all accurately, reports 70, 480, 18, 15 and 90 mm. of water in the 5 dogs measured. When measured with the mercury manometer the pressure was always higher, comparatively, a difference which he ascribes correctly to the loss of fluid into the manometer tube. Falkenheim and Naunyn (19) report the fluid pressure as exceedingly variable: the pressure usually varied between 30 and 38 mm. of water, but they found one dog with 140 mm. of water pressure, another with 75 mm. and another with 15 mm. They believe the pressure to be independent both of the size of the animal and the arterial pressure. Hill (18, p. 73) says: "In normal conditions the pressures generally are 100 to 130 mm. of water." Dixon and Halliburton cite figures about as follows: 190 mm.

10 per cent magnesium sulphate, 45 mm. normal saline; others with 150, 150, 150, 180, 80 and 60 mm. were observed. The exact amount of this pressure, therefore, and its relationship to the venous and arterial pressures is still a matter of some doubt, because there are wide variations in the figures given by the various workers, and in different experiments by the same worker. As can be seen from our work, the reason for such variations is the fact that the pressures normally vary within wide limits in different animals. The best that can be done is to give the readings from a large number of animals and the average from these experiments. See table 2, where we record the first measurements of arterial, venous, and fluid pressure in thirty-nine animals measured according to the method described above. As can be seen from the table the average arterial pressure was 128.79 mm. of mercury, the average venous pressure was 124.97 mm. of sodium carbonate (1.088), and the average cerebrospinal fluid pressure was 112.25 mm. of sodium chloride (1.088). The highest pressure observed in the fluid was 242 in 12, and the lowest was 43 in 219; the highest venous pressure was 425 in 155, the lowest was 44 in 219. It is obvious that the venous and cerebrospinal fluid pressures vary within wide limits, in different animals, even if the same methods are used in making the measurements. This accounts for the wide difference in the figures cited in the past, and shows that the pressure limits are by no means fixed. Twenty-six of the thirty-four dogs measured were below the average given.

We are fully aware of the fact that the figures in our table differ in one essential detail from those given in the past for in nineteen of our thirty-nine dogs the fluid pressure is higher than venous pressure. Hill says: "The intracranial (c.s.f.) pressure has been found in all physiological conditions to be the same as the venous pressure," and adds: "By no physiological means can intracranial pressure be maintained higher than cerebral venous pressure" (p. 68). The data afforded by our experiments shows that Hill's conclusions regarding the equality of the intracranial and venous pressures are not substantiated by our experiments. Either may be higher than the other, but under normal conditions the differences in pressure are small, and the variations in pressure in experiments free from error usually occur in the same direction, although not always exactly to the same degree. Therefore, since our findings are based on experiment, Hill's conclusions on theoretical grounds from experiments on absorption, we are forced to the conclusion that his statement is in error. Frazier and Peet (14) hold venous and fluid pressure to be identical.

TABLE 2

The normal levels of arterial, venous and fluid pressures. This table shows the first readings on 39 dogs and represents, therefore, the normal levels of the arterial, venous and fluid pressures.

TRACING NUMBER	ARTERIAL PRESSURE	VENOUS PRESSURE	C. S. FLUID PRESSURE
	mm. of Hg.	*mm. sod. carb.*	*mm. sod. chlor.*
3	153	136	143
5	134	77	109
6	123	75	82
7	154	322	187
8	138	85	96
9	130	125	158
10	116	87	84
12	146	272	242*
14	112	285	104
15	114	81	95
17	112	102	77
18	132	105	125
20	168	56	44
150	130	262	211
151	176*	118	214
155	153	425*	169
171	142	84	56
174	108	205	98
184	140	116	96
192	124	141	123
197	148	150	99
214	110	72	83
216	130	55	113
219	104	44†	43†
229	108	75	72
230	130	208	90
231	100	63	68
243	120	78	109
258	154	98	140
267	124	127	97
274	92†	46	61
277	88	67	56
279a	160	108	160
279b	124	98	97
280	100	82	100
281	122	87	95
282	170	90	106
283	90	95	110
284	144	72	166
Average.....	128.79	124.97	112.25

* Highest pressure.

† Lowest pressure.

In consequence of what we have shown the last part of the following statement made by Dixon and Halliburton (12) is not correct: "One law always holds, however, under ordinary conditions, the arterial pressure is higher than the venous pressure, and the venous pressure than the cerebrospinal fluid pressure." This law does hold for some of the cases; but numerous variations are seen in which the fluid pressure is higher than the venous pressure in the torcula. We have seen this so often in our experiments that we are confident that it cannot be an error due to manipulation. As may be seen in table 2, in which the data from thirty-nine dogs is listed, when the observations were begun the pressure was higher in the venous blood than in the fluid in twenty cases, the pressure was higher in the fluid than in the venous blood in nineteen cases.

We do not believe that a fluid pressure much higher than the venous pressure is normal, but it does happen frequently that a pressure in the fluid higher by a few millimeters than in the venous pressure is found. Observations with the fluid pressure much higher than the venous pressure were made; in most but not all of these cases epidural or subdural hemorrhages were found. Why an epidural hemorrhage should cause a higher fluid pressure will become evident later. Such a hemorrhage is usually but not always of arterial origin. For that reason we found it best always to discontinue an experiment when a great increase of the fluid pressure over the venous pressure was observed as well as in cases where the venous and fluid pressures were always equal. The latter observation always means a communication between the subarachnoid space and the sinus. On the other hand cases were found in which such a communication existed, but in which the pressures were not the same at any time in the experiment.

Since our results are not in agreement with those of our predecessors we must point out errors in their experiments which we were able to avoid. We believe that we can do this satisfactorily. Neither of the authors quoted above mention at any point in their papers the size of the manometer tubing used in their measurements. Leyden, practically the first investigator to measure the fluid pressure carefully, pointed out the importance of the loss of fluid into the tube in the determination of fluid pressure. He ascribes the lower readings obtained from the water manometer as compared with readings obtained with the mercury manometer in the same animal to this cause. His objections and views in the matter are correctly taken. Of course if care is taken to adjust the level of the fluid in the tube to such a height as to balance the pressure

in the canal, before the latter is connected with the manometer, so little or no fluid can escape from one to the other, then the first reading will be approximately correct. However, even if this precaution is observed, error can not be avoided later in the experiment if a large bore manometer is used, an error becoming progressively greater the farther the pressure in the canal varies from the normal. Therefore we conclude: if a large bore manometer is used a correct estimate of the pressure of the fluid can be obtained only if the adjustment of the fluid to the pressure in the canal is nearly perfect at the time the needle is pushed into the canal.

If this situation holds for the normal pressure, it is clear that with rising or falling pressures, this factor becomes more important the farther the pressure deviates from the normal. A consideration of the situation shows: Under ordinary conditions where there is an abundance of fluid to supply the apparatus when the pressure is rising, and an abundance of room to accommodate the fluid when the pressure is falling as is the case in the vascular system, the bore of the manometer used in making pressure measurements is of no importance. This holds true in taking venous pressures, for in the cerebral venous system there is an abundance of blood available from the general circulation to supply the manometer tube, when the pressure is rising, and plenty of space to accommodate the excess of fluid when the venous pressure is falling. On the contrary, when dealing with a situation where the amount of fluid as well as the space to accommodate fluid is limited, as is the case with the cerebrospinal fluid and the dural canal, the bore of the manometer *is* of importance. With the escape of the fluid from the canal into the tubing while the pressure is rising, the observer will measure not the normal pressure in the canal with the normal amount of fluid, but the pressure in the canal less the pressure which would have been produced by the amount of fluid lost into the system of tubes. When the pressures fall below the normal, he measures not the pressure in the canal under a similar condition in the intact animal, but the pressure in the canal increased by the amount due to the excess of fluid entering from the manometer tubes. For this reason a large bore manometer will measure the true pressure of the venous blood in the sinuses, but will not measure the true pressure in the fluid under normal conditions in the dural canal, if the pressure varies in any degree either above or below the initial level at which the observations were begun. To test out the validity of this point we performed the experiments shown in table 3.

This table shows clearly that the bore of the manometer influences markedly the results obtained in the measurements of the pressure of the fluid. This does not hold true to the same degree for venous pressure measurements. The fact that the tracings shown by Hill and by Dixon and Halliburton, show wide excursions of the tambour levers, is evidence that their manometers were fairly large, and for that reason their records of the fluid pressure where the pressure is rising are too low, where the pressure is falling too high. Because in the former case a part of the fluid flows out to fill the tube partially emptying the canal and reducing the final pressure below what it would have been if the

TABLE 3

Influence of the bore of the manometer on the readings of venous and cerebrospinal fluid pressures. (All three manometers were connected before beginning any of the readings with the fluid level at zero. The measurements were made by opening the clamp to 1, and taking the reading; the fluid was then forced back into the canal so the fluid stood at zero, and the clamp was closed; 2 and 3 were then read in the order named. Manometer 1 had a bore of 1 mm.; 2, 5 mm.; 3, 8 mm.)

	GENERAL ARTERIAL	TORCULAR VENOUS			C. S. FLUID		
		Manometer number					
		1	2	3	1	2	3
Normal	102	127	115	115	97	89	89
During occlusion of the jugulars	100	237	236	230	157	96	90
Normal after release of jugulars	98	126	110	110	94	90	84
Normal	160	445			162	54	27
Normal	160	401			95	44	15
Normal	84	116	119	116	60	11	11
Normal	160	90	80	79	36	37	35
Occlusion of jugulars	160	204	173	172	110	81	57

normal amount of fluid had been in the canal; in the latter the fluid flows from the tube into the canal overfilling it, and raising the pressure above what it would have been if the normal amount of fluid had been in the canal.

On the other hand the conclusions of Wegefarth (20) from the work of his predecessors as expressed in his statement (p. 164): "It seems probable that in both situations (the eye and the brain) the fluid pressures are constantly being reduced to the level of the venous pressure in the great sinuses, and that, because of the resistance of the complex fluid pathways the fluid is constantly at a higher pressure than in the sinus,"

are not warranted by our findings nor the findings of our predecessors. Since it is certain that venous pressure usually is—some say always—higher than cerebrospinal fluid pressure, it is self-evident that the establishment of a free communication between the venous sinuses and the subarachnoid space with the idea of furnishing a pathway of escape for the fluid in the case of hydrocephalus as suggested first by Gaertner (21), and modified later by McClure (22), Haynes (23) and Wegefarth, is not an operation to be undertaken lightly in man because of the obvious dangers of subarachnoid clot formation and its sequellae as soon as the pressure in the skull falls to the normal.

Our final conclusion regarding the levels of arterial, venous and fluid pressures are: Venous and fluid pressures are always less than arterial pressure. Venous and fluid pressures are almost but not exactly equal, but no fixed law can be given in regard to which is under the greater pressure. The differences when great are in favor of the venous pressure, and we find a good many normal animals in which the venous pressure is considerably higher than the fluid pressure (100 mm.). In our series of thirty-nine experiments here listed, seven animals with such pressure relations were found. The use of a manometer with a wide bore led to the failure of earlier workers to discover that venous and fluid pressures are not identical, and that it is physiologically possible at least in the dog for the fluid pressure to be higher than venous pressure.

2. The normal variations in the arterial, venous and cerebrospinal fluid pressures in the anesthetized animal

Having established the normal levels of arterial, venous and fluid pressures it is necessary to study the variations undergone by these pressures during a long experiment to see how the pressures of these fluids are modified by continued anesthesia. Further, it is essential to see whether the initial levels of these pressures are representative values, for it is conceivable that they are subject to such wide independent variations that the initial levels are not significant in the least degree.

Literature: Hill believes the intracranial (p. 71) "is the same as the cerebral venous pressure, and varies in the same direction absolutely as general venous pressure, and proportionately as general arterial pressure". . . . (p. 72). The "cerebrospinal fluid pressure does not always absolutely correspond, since the brain . . . . on expansion expresses the cerebrospinal fluid from the cranium and comes in contact with the cranial wall."

Dixon and Halliburton (12) in their discussion of the normal fluid pressure cite in detail an experiment which gives the impression that very great differences exist between the venous and the fluid pressures, normally, and that wide variations in the fluid and venous pressures are common. At the beginning of, and during an experiment lasting 75 minutes, these pressures showed wide variations. Summarized the experiment is as follows:

	BEGINNING	AT 35 MINUTES	AT 65 MINUTES	AT 75 MINUTES
	mm.	*mm.*	*mm.*	*mm.*
Venous	350	415	330	255
Fluid	95	65	50	90
Difference	255	350	280	165

It should be noted that between the first and second observations the venous pressure rose and the fluid pressure fell; between the second and third, they both fell; between the third and fourth the venous pressure fell and the fluid pressure rose. Without citing definite figures the authors say that this experiment is typical of all other experiments. Thus venous and fluid pressures varied twice in opposite directions and once in the same direction in three observations.

TABLE 4

This table shows the variations in pressure in an animal under anesthesia for three hours. Observations were made at 15 minute intervals

	1	2	3	4	5	6	7	8	9	10	11	12	13
General arterial	90	100	106	104	106	112	112	112	116	114	120	128	128
Circle of Willis	72	78	84	82	84	86	88	92	98	98	92	110	106
Torcular	95	92	78	87	105	130	145	112	128	115	182*	99	146
Fluid pressure	110	99	81	88	89	111	137	109	128	116	192	104	145
Venous minus fluid	−15	−7	−3	−1	16	19	8	3	0	−1	−10	−5	1

* Cause of marked venous and fluid rise at this point not clear.

We have made observations on a large number of animals. In order to bring out the characteristics of our observations we will present the variations in detail in one animal. (See table 4.)

As can be seen from table 4 there is a gradual slow rise in all the pressures from the beginning to the end of the experiment. The arterial rise is gradual and steady; the fluid and venous pressure underwent

numerous fluctuations, but after the first 30 minutes the tendency toward a rise became well marked. The remarkable parallelism between venous and fluid pressures shows clearly in figure 2, which was obtained by plotting the readings on coördinate paper. The differences between venous and fluid pressures are much smaller than those reported by Dixon and Halliburton, the variations in venous and fluid pressure are more nearly proportional than reported by them and unlike in their experiment, they vary in the same direction in every instance. There are in this experiment no exceptions to this rule.

To confirm the data from this single experiment we give table 5.

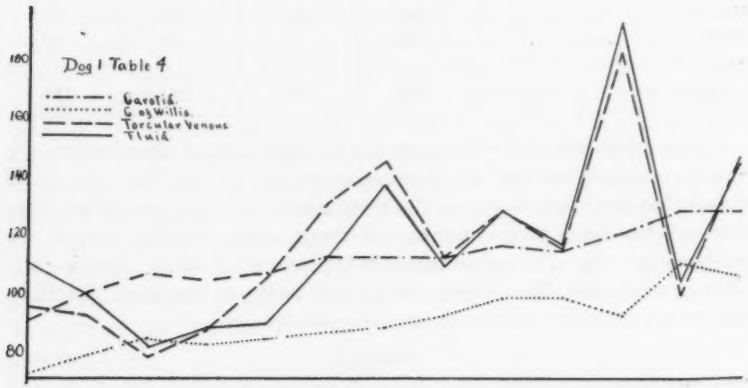

Fig. 2. This figure shows the alterations in pressure in the arterial, venous and fluid system during a long period of observation. No manipulations were performed throughout the whole period.

This table shows readings taken at 15 minute intervals from five dogs selected at random from our series of long time experiments. These variations should then be illustrative of the facts regarding the variations in the pressures in animals, in which mild changes were produced, and the animals were kept long under observation, and these constitute the controls for the whole work. As can be seen the variations in these five animals are practically similar with the variations in the single animal cited in table 4.

It is evident from the data in our tables that we cannot agree that the data in the experiment cited by Dixon and Halliburton is typical of a large number of experiments. In our experience the average fluid and venous pressures are much more nearly equal than in the experience

TABLE 5

This table shows the variations of the pressures in animals under experimental conditions. Readings were made at 15 minute intervals. Note the variations in the relations of venous and cerebrospinal fluid pressures, either may be higher than the other, but closely follow each other. Arterial pressure in millimeters of Hg., venous pressure in millimeters of sodi. carb. (1.088); cerebrospinal fluid in millimeters of NaCl (1.088). Tissue extracts were administered between readings

DOG NUMBER		OBSERVATION									
		1	2	3	4	5	6	7	8	9	10
1	General arterial.....	154	126	160	136	156	160	146	142	82	
	Circle of Willis.....	116	118	128	130	142	140	134	132	70	
	Torcular venous.....	87	101	130	67	65	66	61	59	44	
	Fluid pressure.....	84	95	115	48	42	51	56	64	49	
	Venous minus fluid pressure.....	3	6	15	21	13	15	5	−5	−5	
2	General arterial.....	130	118	116	120	122	116	100	82	88	80
	Circle of Willis.....	119	105	100	99	107	104	90	73	72	72
	Torcular venous.....	125	97	105	113	109	99	112	82	93	92
	Fluid pressure.....	158	131	139	140	132	116	137	111	116	115
	Venous minus fluid pressure.....	−33	−34	−34	−27	−23	−17	−25	−29	−23	−23
3	General arterial.....	146	128	146	148	152	156	152	126	114	
	Circle of Willis.....	90	80	84	118	118	116	102	76	66	
	Torcular venous.....	272	246	276	301	307	319	296	251	234	
	Fluid pressure.....	249	228	257	270	282	292	287	245	228	
	Venous minus fluid pressure.....	23	18	19	31	25	27	9	6	6	
4	General arterial.....	124	120	124	132	130	120	122	130	124	122
	Circle of Willis.....	96	96	94	100	104	98	96	104	100	92
	Torcular venous.....	75	75	78	83	65	53	50	54	55	71
	Fluid pressure.....	82	77	79	85	69	53	47	48	52	65
	Venous minus fluid pressure.....	−7	2	−1	−2	−4	0	3	6	3	6
.5	General arterial.....	138	148	140	150	178	152	162	156	154	137
	Torcular venous.....	85	124	90	95	114	59	88	111	118	105
	Fluid pressure.....	96	131	105	88	132	48	79	115	117	106
	Venous minus fluid pressure.....	−9	−7	−15	7	−18	11	9	−4	1	−1
Average from Dogs 1 to 5											
Average..	General arterial.....	138	124	137	137	147	141	136	127	112	113
	Circle of Willis.....	105	100	101	112	118	114	105	96	77	82
	Torcular venous.....	129	129	136	132	132	119	121	111	109	89
	Fluid pressure.....	134	132	139	126	115	112	121	117	112	95
	Venous minus fluid pressure.....	−5	−3	−3	6	17	7	0	−6	−3	−6

of Dixon and Halliburton. We have a much closer parallelism between the changes in the two pressures than is shown by their experiments. In our experiments, as can be seen by reference to the tables, the variations in the normal animal are almost always in the same direction and are to some degree proportional. The variations in all the pressures are greater in the experiment of Dixon and Halliburton than those seen in the animal under simple anesthesia. If these figures shown by these authors were typical, if the pressures were subject to variations as wide as those recorded, if the pressures lacked the parallelism of change to the degree their experiment shows, then it would be useless to go farther, for it would be impossible to draw any conclusions from experiments on this subject for the normal variations would be so wide as to render conclusions from experiments of no value. Our results show that the pressures are much less variable, and that the pressures vary much more nearly in the same directions and to the same degree. To be specific: In the 58 simultaneous changes shown in table 5 above, the pressure of venous blood and fluid varied in the same direction 50 times, in opposite directions 6 times, and in 2 instances one varied and the other remained stationary. In the same 58 changes arterial and venous pressure varied in the same direction 37 times, in opposite directions 16 times, and in 5 cases one remained unchanged while the other changed. In the same 58 readings arterial and fluid pressure varied in the same direction 39 times, in opposite directions 15 times, and in 4 cases one remained stationary while the other changed. It is thus self-evident that fluid pressure follows venous pressure more closely than it follows arterial, and also that venous and fluid pressure vary in the same direction and these variations are to some degree proportional.

Our variations in the pressure level of fluid is considerably wider in the individual animal than those reported by Weed and McKibben (36) in their recent article on fluid pressures. However, these variations add to rather than detract from the proof that the fluid follows venous rather than arterial pressure variations. Further, our composite curve of five animals, if plotted from table 5, would compare very closely to the curve they show as the composite of seven animals.

3. The influence on the fluid pressure of raising and lowering the venous pressure

As has already been shown, the pressure of fluid in the canal is always positive under the conditions we have studied. The sources of this positive pressure must now be investigated, and if more than one force

contributes, then the relative importance of each must be determined by experimental, not theoretical, means. Unfortunately it is not always possible to secure a change in one factor at a time, leaving all the others constant, for any manipulation changing one, modifies to some degree one or more of the others. Hence the experimental proofs are not purely objective, and are weakened by the errors common to the interpretation of complicated experiments. In considering the origin of the positive fluid pressure, the following sources must be emphasized: *a*, arterial blood; *b*, venous blood—either or both of these may transmit pressure to the fluid through the walls of the vessels; *c*, alterations in the volume of the brain, from gain or loss of blood or other fluid by that organ; *d*, secretory pressure from the activity of the cells elaborating the fluid, thus forcing the accumulation of the fluid into a confined space, the canal. Any or all of these forces may be active in modifying the pressure under which the fluid is found. The influence of the factors enumerated is modified by the amount of fluid in the canal, and hence by the rate at which the fluid is formed and removed. The inter-relations of the arterial, venous and fluid pressures were studied by noting the variations in these pressures in an animal under ether for a long time without any other manipulations than those essential to the connection of the necessary apparatus, and by observing what effect modifying one at a time or two at a time had upon those remaining.

Literature: So far as we are able to cover the literature, Falkenheim and Naunyn (19) were the first to study the influence of raising the venous pressure on the pressure of the cerebrospinal fluid. They produced this result by blowing up a rubber balloon in the right ventricle. They noted in two of the cases a rise in fluid pressure; in the third, a fall. In the first two cases reported the arterial pressures were low, 105 to 120, in the third the arterial pressure was high, 210, and they concluded that the rises were due to venous stasis without much reduction in cardiac output, while the fall was due to a fall in arterial pressure due to the marked reduction of cardiac output because of the pressure of the balloon. These explanations are probably correct, although so far as the tabular report of the experiment is concerned neither venous pressure nor arterial pressure is recorded.

Dixon and Halliburton (11) in their first article dealing with the outflow of fluid under the influence of depressor substances in general and choroid extract in particular, eliminate the factor of the venous pressure by argument, not by experiment. They say (p. 240) in regard to depressor substances: "It might be argued that the fall of blood pres-

sure in the arteries will be accompanied by a rise in the veins. . . . This argument may be met in the following ways: (1) increase in the venous volume will be counteracted and probably counterbalanced by decreased arterial volume, so the change of brain volume will be negligible; (2) the fall of arterial pressure is not always seen; and (3) other substances which cause a depressor effect do not increase the cerebrospinal flow." That this argument will not hold will be shown in the experimental part of the paper.

In their second paper (12) these authors had come to recognize the important influence of venous pressure on the fluid pressure. Thus they noted (p. 141) that a rise in venous pressure produced a rise in fluid pressure. "It will be noted that in each instance the rise in C. S. pressure is only about one-quarter that which occurs in the torcular." They say further (p. 142): "If arterial and venous pressures are lowered, as for example by bleeding, the drop in C. S. pressure is relatively small." They state further from experiment that the alterations in fluid pressure and venous pressure are not synchronous nor proportional, and hence independent of each other; and state in their conclusion: "The C. S. pressure is influenced passively to a small extent by changes in arterial and venous pressures, but such alterations are insignificant compared with the independent changes in pressure which occur as the result of secretory activity."

In their third article these authors study the effect of increased intracranial pressures upon the circulation and respiration. In addition to studying the effect on the various centers of the medulla they attempt to draw conclusions regarding the rate of blood flow through the brain by study of the rate of flow from the "cerebral end of the cut left internal jugular vein."

Frazier and Peet (7) state: "The pressure of the cerebrospinal fluid is under normal conditions identical with venous pressure, conditions affecting venous pressure . . . . should disturb the pressure of the cerebrospinal fluid." From experiments briefly cited they conclude: "The pressure of the cerebrospinal fluid drops to zero after occlusion of the carotid circulation only to recover itself in a very few minutes, while occlusion of the venous circulation is followed by a rise in pressure more or less constant. . . . . The more or less constant rise in pressure when the venous circulation is interrupted confirms the hypothesis that the absorption of cerebrospinal fluid takes place chiefly through the venous channel."

In a second paper (14) they state: "The administration of any depressor substance such as extract of spleen, ether, amyl-nitrate (nitrite?) or magnesium sulphate caused a marked drop in arterial pressure followed by a slow rise to normal. Practically coincident with this drop in arterial blood pressure was a sudden rise in the cerebral sinus pressure. This usually occurred immediately after the sudden drop, and not with it. The sinus pressure continued to rise as long as the arterial blood pressure remained at its lower level. As the femoral pressure gradually returned to normal the sinus pressure slowly dropped." They conclude: "The sudden increase in the rate of outflow following the injection of organ extracts is the result of sinus distension which forces out fluid already present in the ventricles and cisterna."

Weed and Cushing state: "In view therefore of the possible influence of these physical factors (alterations in capillary pressure due to changes in arterial and venous pressure produced by the injection, and the possibility of fluid displacement by the accumulation of venous blood) on the discharge of cerebrospinal fluid, it is hazardous to assume that certain agents stimulate the secretion of the choroid plexuses, merely because of an observed increase in flow from a cannula."

Dandy and Blackfan (24) describe a series of experiments in which they attempted to increase the fluid outflow from a cannula inserted into the canal through the atlas. They state: "The most striking and uniform result obtained . . . . followed temporary compression of the jugular veins. Except in one instance there was always a marked and instantaneous increase of cerebrospinal fluid following jugular compression. We believe this can be explained only by an increased production of fluid."

Experimental: A study of the influence of the venous pressure can be carried out almost uncomplicated by alterations in the arterial pressure. This can best be done by ligation of the jugular veins. Ligation of the internal jugulars alone in most animals produces little effect, either upon the venous or the fluid pressure. In a very small percentage of cases a rather marked rise in the venous and the fluid pressure will follow such a ligation. (See table 6.) This is of course in keeping with the findings of Gärtner and Wagner (25). Unless otherwise specified, the term "ligation of the jugular" means ligation of the external ones only. The effect of the ligation of these veins upon the arterial and fluid pressures can best be shown by the use of tables. (See tables 6 and 7 and figs. 3, *A*, *B* and *C*, and 4).

TABLE 6

Effect on the various pressures of ligation of internal and external jugulars successively and simultaneously

			GENERAL ARTERIAL				TORCULAR VENOUS				C. S. FLUID			
			B.	D.	A.	Rise or fall	B.	D.	A.	Rise	B.	D.	A.	Rise
226	a	Internal jugulars ligated	130	128	130	−2	208	226	207	18	90	93	84	3
	b	External jugulars ligated	124	122	130	−2	201	230	209	29	81	101	78	20
	c	Both pairs jugulars ligated	130	128	134	−2	201	237	188	36	75	99	72	24
279	b	Internal jugulars ligated	162	154	160	−8	108	120	108	12	166	175	165	9
	a	External jugulars ligated	160	160	160	0	108	240	108	132	160	241	166	81
	c	Both pairs jugulars ligated	162	150	160	−12	108	280	104	182	165	267	160	102

TABLE 7

Effect on the arterial and fluid pressures of the ligation of the jugular veins

TRACING	ARTERIAL			CIRCLE OF WILLIS			TORCULAR VENOUS			C. S. FLUID PRESSURE		
	B.	D.	A.	B.	D.	A.	B.	D.	A.	B.	D.	A.
153	158	150	160	120	118	120	601	706	625	141	237	129
154	118	108	120	90	88	92	354	412	353	113	191	104
155	152	142	130	114	112	102	425	796	496	189	321	195
156 a	130	116	122	102	100	100	496	579	479	195	250	168
156 b	122	116	112	100	98	96	484	560	529	164	210	145
158	114	108	118	88	86	90	356	477	357	122	191	112
160	156	150	158	132	140	142	58	271	79	60	195	65
161	120	110	120				150	420	124	201	403*	193
152 a	176	166	140	146	140	126	118	401*	217	214	321	229
152 b	104	104	110	84	84	88	86	166	92	264	317	288
152 c	94	94	102	80	82	84	66	143	72	109	161	105
152 d	42	42	46				38	70	39	69	90	75
171a	142	138	140				84	125	88	56	84	54
197	148	150	162				150	324	165	99	213	120
200	158	150	158				142	295	155	108	195	108
226b	124	122	130				201	230†	209	81	101†	78
279a	160	160	160				108	240	108	160	241	166
158a	130	134	128	112	120	112	262	504	290	211	393	220
Average...	130.4	125.5	128.6	106.1	106.1	104.7	232.1	371.7	248.7	142.0	228.5	141.8

* Greatest change from normal.

† Least change from normal.

Table 7 shows clearly that a rise in the venous pressure produced by the ligation of the jugulars is accompanied in every case by a rise in the pressure in the fluid. The rise in the latter is not so great as in the former, and these differences vary in the different animals, but the rise in the venous pressure, if great, is accompanied by a pronounced rise in the fluid pressure; if small, by a small rise in the fluid pressure. It is also to be noted that the changes are diphasic. The venous and fluid pressures rise and fall almost, in the best experiments absolutely,

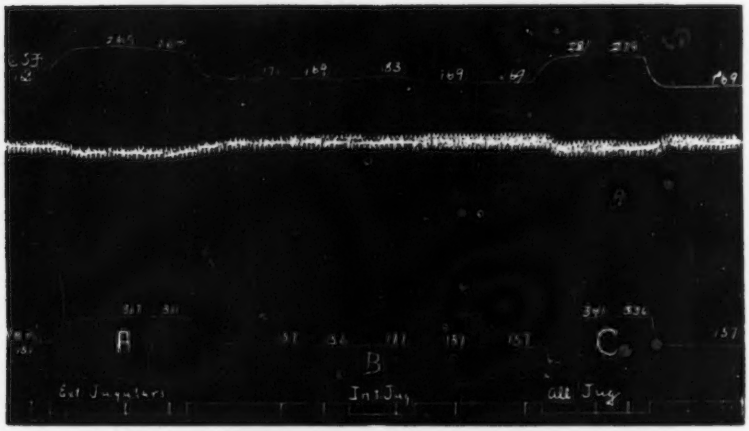

Fig. 3. This figure shows the differences in the reaction of a dog to ligation of the internal and external jugulars. It shows: *a*, the greater effectiveness of ligation of the external jugulars than ligation of the internal jugulars in raising venous and fluid pressures; *b*, the striking similarity in the curves of venous and fluid pressure, both as regards the time relation and the shape of the curves. The numbers represent millimeters of a solution with a specific gravity of 1.008. In this and in later tracings, *V* designates the torcular venous, *F* the C. S. fluid pressure.

synchronously. As can be noted from the figure, there is tendency for the fluid rise to lag behind the venous rise. The same holds true for the fall, a phenomenon which has an easy explanation in the greater complication of the system of canals through which the fluid must pass both in leaving and in reëntering the canal. The amount of delay varies widely between different animals. It is also to be noted from figure 4 that the height of the rise following ligation of the veins is dependent largely upon the height of the arterial pressure. If the latter

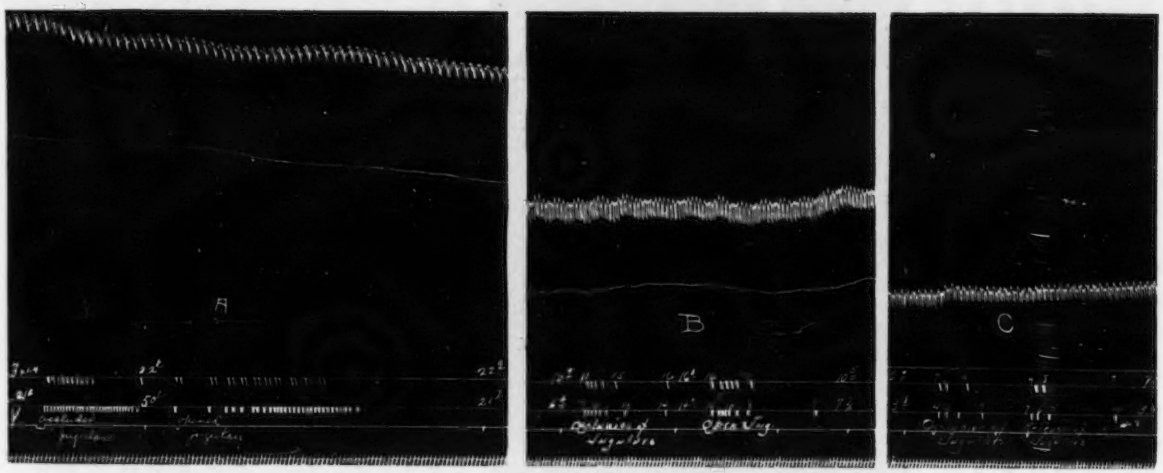

Fig. 4. This figure shows the variation in the result upon venous and fluid pressure of occlusion of the external jugular veins: *A* shows the result early in the experiment; *B*, the result 1 hour and 15 minutes later; *C*, the result 2 hours and 20 minutes later.

is high, occlusion of the veins produces a marked rise in the venous and fluid pressures; if low, ligation of the veins produces a small effect. This can be seen readily by reference to figure 4. In this figure we have the effect of three ligations in the same animal. The first was early in the experiment with a high blood pressure. It produced a great rise both in the venous and the fluid pressures. The second was in the middle of the experiment, the pressure had fallen in the artery, and the effect of the ligation of the vein was to raise the pressure in the sinus

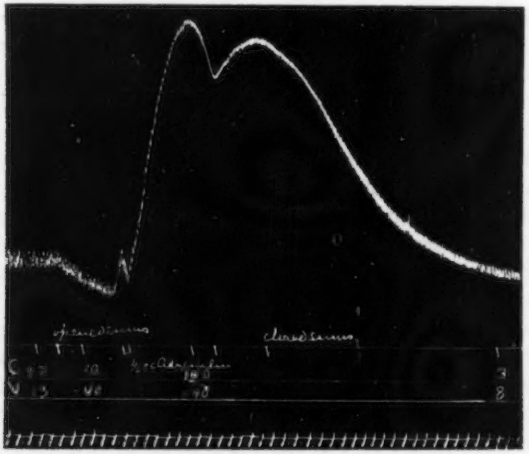

Fig. 5. This figure shows that when the sinus is opened so that the torcular pressure falls from 13 to −40 mm. (53 mm.), the fluid pressure falls from 22 to −10 mm. (32 mm.). The remainder of the tracing was a study on another phase of the subject, and is given only to show that the venous pressure rose to 8, the fluid pressure to 3 mm. after the sinus was closed and the effect of adrenalin had passed off.

and the fluid considerably but not nearly so much as in the first ligation. The third was at the end of the experiment, the arterial pressure was low and the effect on venous and fluid pressures was slight, almost negligible.

Further, lowering the normal venous pressures in the skull by opening the sinus results in a fall of the fluid pressure. (See fig. 5). Table 1 and figure 1 show that cerebral venous and general venous do not vary to the same degree or even in the same direction.

Since a rise in venous pressure always produces a rise in fluid pressure, and a fall in venous pressure always produces a fall in fluid pressure, it is self-evident that in any experiment the cerebral venous pressure must be measured *during the experiment* to eliminate the possibility of a venous pressure change before increased formation or absorption can be *proved.*

A study of the influence of torcular venous pressure upon the pressure of the cerebrospinal fluid makes it evident that any experiment involving the use of a drug, or any physiological manipulation which has the least possibility of producing changes in the venous pressure, is worthless unless the venous pressure in the sinus, not in the general circulation, is measured as well as the arterial and fluid pressures. The marked influence of venous upon the fluid pressure is so easily established, and its significance is so unmistakable, that it is surprising that any recent worker would neglect the measurement of this important factor in any experiment from which he intends to draw conclusions regarding the nature of the change in the fluid pressure and the fluid formation. If limited to the measurement of one of these besides the cerebrospinal fluid pressure he would do well to measure the venous pressure rather than the arterial, because of the relatively greater importance of the former than the latter in the determination of the fluid pressure. The fact that Frazier and Peet, Dandy and Blackfan, and Weed and Cushing in their work failed to record this pressure in a single one of their experiments, and that Dixon and Halliburton (12) in their work on the choroid, measured arterial and venous pressures in one animal or experiment, and arterial and fluid pressures in another, and took it for granted that the behavior of the venous pressure was the same in both cases—when such was not necessarily the case at all—detracts markedly from the value of their work.

Let us take up more in detail the criticism of the experiments found in the literature. We believe that the authors mentioned failed to measure the venous pressure simultaneously with other pressures, because they underestimated its influence on the fluid pressure. Dixon and Halliburton say: "The rise in C. S. pressure is only about one-quarter that which occurs in the torcula . . . . . when the two pressures are low the passive effects of increasing the venous pressure is negligible." Thus these authors while admitting that increasing the venous pressure passively increases the fluid pressure, do not find the increase in the latter to any degree comparable to the increase in the former. In our work, making use of a manometer with a fine bore, as

can be seen from the table, the changes in pressure in the venous and fluid systems are much more nearly equal than in the few experiments cited by Dixon and Halliburton. We are convinced that if we could measure the fluid pressure at the crest of the venous rise as accurately as we can at the bottom without permitting the escape of fluid into the manometer tube, the changes in fluid pressure would almost if not quite equal the changes in venous pressure. Their error lies in the fact that they used a piece of apparatus not adapted to the needs of the experiment, with the result that they did not measure the pressure in the normal intact animal, but the pressure change in an animal with the pressure reduced by the withdrawal of an amount of fluid necessary to fill the tube of the manometer to the required level. They failed to note also that if venous pressure is low the arterial pressure may be relatively high, and that when this is the case obstruction of the venous outflow or ligation of the veins is followed by a great rise both in the venous and fluid pressures, for it is the "highness" of the arterial pressure, not, as they state, the "lowness" of the venous pressure which determines the amount of rise in the venous pressure following occlusion and, therefore, the amount of rise in the fluid pressure. (See fig. 4. Compare also the results in tracing 152 a, with 152 d, table 7).

Nor can we concur in the statement made by the authors that: "Perhaps the most remarkable feature of the cerebrospinal fluid viewed from the physical side is the fact that relatively small circulatory changes as determined by the general arterial and venous pressures may cause large changes in the cerebral venous pressure, but have little effect on the cerebrospinal fluid pressure." As we have already said, the general venous and the torcular venous are practically independent of each other, they vary in the same or in opposite directions as is shown fully in table 1 and in figure 1. But in the measurements shown in the table, in only one case was the general venous higher than the torcular venous. We used the brachial vein in preference to the right heart because of the fact that the technic in using the former is less cumbersome, and the balloon in the auricle must dam the blood back into the great veins to some extent, and what is more dangerous, to a varying extent. The fluid pressure nearly always—in fifty of fifty-eight cases—varies in the same direction as the cerebral venous pressure, and in some degree proportionally.

Further we observe, as they have done, great changes in the torcular venous pressure without a corresponding change either in general ar-

terial or venous pressures. Extreme care must be observed in this work; a rise in general venous pressure usually gives a rise in the torcular pressure; movements of the head, perhaps shifting the muzzle only a few inches will raise the torcular pressure 30 or 40 mm. probably by occluding the jugular veins in the neck. The observation was made long ago that shifting the head would raise the fluid pressure (16). The explanation given by this writer was that the lateral movements of the spine narrowed the space available for the fluid and thus increased the pressure of the fluid in the canal. The increase in venous pressure invariably increases the pressure of the fluid. Placing the hand on the neck or on the abdomen has the same effect. In the experiments which we performed and considered free from error, any rise in the venous pressure in the torcula was always accompanied by a rise in the fluid pressure. Therefore, the last statement in the quotation above is an error, for as can be seen from our experiments on venous occlusions, the cerebral venous pressure invariably *does* influence the fluid pressure directly. If this is true for venous pressure raised passively, it is true also for the pressure rises in venous blood, whether caused by drugs or other agencies.

From the conclusions of Frazier and Peet regarding the influence of the venous pressure on the fluid, it is evident that they also underestimate the importance of this factor. A rise of 40 mm. in fluid pressure is not as much as is to be expected on ligation of the jugular vein if the animal is in good condition. The rises in our experiments averaged 86 mm. We do not know the diameter of the manometer tube they used, so cannot judge whether the error is in the apparatus or is to be ascribed to some other source. However, in our experiments, animals long under ether anesthesia showed practically no rise in the venous pressure on ligation of the veins, because the arterial pressure was too low. This may have been the cause of the small rise they record; or, morphine-urethane anesthesia pushed too far would produce the same results. The fact remains that ligations such as they decribe, carried out in fresh animals under a proper degree of anesthesia, show the results given in table 7, which records the effects on the venous and fluid pressure of the ligation of the jugulars in eighteen animals. It will be seen that the greatest change in venous pressure was in no. 152 a, where the venous pressure rose 383 mm. of sodium carbonate, while the fluid pressure rose 132 mm. of NaCl. The greatest change in fluid pressure was in no. 161, where while venous pressure rose 270 mm. of sodium carbonate, fluid pressure rose 202 mm. NaCl. The smallest rise was in no. 226 a,

where the venous rise was 18 mm., the fluid rise 3 mm. The average for the whole series was arterial rise −4.9; venous 139.6, fluid 86.5. These results show conclusively that the figures reported by Frazier and Peet are too low, hence the importance of the venous pressure in the experiments—a pressure which they mention, but do not record—is enormously increased.

These tables substantiate the statement made by Hill long ago, that an increase in the venous pressure, uncomplicated by any marked change in the arterial pressure, is accompanied by an increase in the cerebrospinal fluid pressure; while a fall in the venous pressure is accompanied by a fall in the cerebrospinal fluid pressure. This proves clearly that in those cases where venous pressure was not recorded the writers do not have all the facts regarding the forces responsible for the changes in the pressure and the outflow of the fluid. This one fact eliminates a large number of recent experiments from consideration. Dandy and Blackfan apparently were not aware of the fact that the outflow of the fluid was only half of the total change in the fluid which occurs on ligation and release of the veins, for under suitable conditions of experimentation the fluid would have returned to the skull in an amount equal to the amount which escaped. They would not have drawn the conclusions they did if they had known that the changes are reversible. The fact which they consider of so much importance, that the original rate of outflow from the cannula was reëstablished after the release of the veins, is of no great significance, for with the release of the veins and the reduction of the venous pressure in the skull, fluid from some other place in the subarachnoid space was released and flowed out of the needle. This explains why repeated ligations and release of the jugulars produced repeated increases in the outflow, as well as the observation that the original rate of outflow was reëstablished. According to our own observations on this point repeated ligations of the veins become progressively less effective in producing fluid.

Having established the fact that the changes in the venous and fluid pressures are in the same direction, more or less equal in amount, and reversible, it is necessary to inquire into the nature and mechanism of the changes. We believe that one of three explanations is the correct one:

1. Increased formation [due *a*, to increased capillary tension; *b*, to increased secretion due to asphyxia,] perhaps complicated by impaired absorption.

2. Increased venous pressure with the accumulation of venous blood in the sinuses and the displacement of fluid; an increased accumulation of venous blood without an increased pressure is possible.

3. Simultaneous but independent rises in fluid and venous pressures.

1. Ligation of the veins increases the capillary pressure in the skull. Because the venous pressure is increased without much reduction in the arterial pressure, filtration is favored, if that be the mechanism of the formation of the fluid. Frazier and Peet (14, p. 484) believe this factor important for pressures over 190 mm. of water in the veins. Weed and Cushing (8, p. 100) say "venous pressures . . . . . may exert considerable effect upon the secretory pressure through alteration in the capillary tension for, as Starling has demonstrated, capillary pressure follows more closely upon alteration in venous pressure than upon far greater changes in the arterial tonus." Ligation of the veins produces venous stasis, and thus asphyxia may stimulate the cells to increased activity, if secretion is the mechanism of the formation of the fluid. The rôle of asphyxia as a stimulus to the cells of the choroid has been strongly emphasized by recent writers (12). In addition to this, since it is evident that the absorption of the fluid is by way of the veins rather than by the lymphatics, ligation of the veins should prevent absorption and thus favor the accumulation of the fluid. Hence the fluid pressure may rise, not only because more fluid is formed, but because less is absorbed from the canal. On this point Frazier and Peet (p. 274) say: "The more or less constant rise in pressure when the venous circulation is interrupted confirms the hypothesis that the absorption of cerebrospinal fluid takes place chiefly through the venous channel. We can show that neither filtration nor secretion need be assumed to explain the facts."

2. The second explanation of the rise in the fluid pressure on ligation of the jugulars is that it is due to the increase in the venous pressure, which permits the accumulation of the venous blood in the sinuses, and displaces the fluid from its usual place in the canal.

In favor of the second we have the observation that the changes in the two pressures are synchronous. And not only are the changes parallel but they are to some degree proportional. (See table 8 and fig. 4). The rise in the fluid pressure is 61 per cent of the rise in the venous pressure, and the fall is 69 per cent of the fall in the venous pressure. This parallelism is confirmed in the work of Dixon and Halliburton. They do not confirm our findings as regards the amount of change: "The rise of the C. S. pressure is one-quarter that which occurs in the

torcula." The explanation of the differences between their observations and our own has already been fully discussed in the section on the influence of the size of the manometer tubes. The failure of Dixon and Halliburton to notice that the venous and the fluid pressures vary much more nearly to the same degree, led them to the erroneous conclusion that "fluid pressure is an independent pressure and the factors determining its height are dependent on the rate of secretion and absorp-

TABLE 8

This table shows the effects on the arterial and venous pressures of increasing the cerebrospinal fluid pressure by small amounts (98 to 202 mm. of NaCl *Sp. Gr. 1088)*

TRACINGS	ARTERIAL			TORCULAR			CEREBROSPINAL FLUID PRESSURE			REMARKS
	B	D	A	B	D	A	B	D	A	
188	150	148	146	120	123	122	93	191	182	Fluid held in canal
189	130	120	120	113	116	135	92	280	127	Drew out 2.5 cc.
190	142	144	142	104	105	105	76	274	104	Drew out 2.5 cc.
191	140	140	140	96	99	103	71	170	76	Drew out 2.5 cc.
192	124	120	106	145	112	125	123	325	137	None drawn off
193	90	90	84	84	92	88	97	254	230	None drawn off
194	92	92	84	61	61	61	91	257	145	Fluid allowed to escape
195	114	146	114	75	63	84	65	260	68	Fluid allowed to escape
196	132	124	118	84	76	66	68	258	183	Fluid allowed to escape
197	106	106	98	54	59	59	88	254	185	Fluid allowed to escape
229a	108	168	112	75	75	63	72	264	65	
229b	112	146	112	63	68	76	65	260	68	
229c	136	124	116	76	76	54	68	258	86	
229d	104	104	98	54	59	59	88	254	185	
231a	96	100	92	63	62	55	68	331	71	
231b	88	96	88	53	64	52	64	331	73	
232	84	96	84	54	67	61	61	324	74	
233	78	92	64	51	56	52	66	343	81	
234	66	60	58	64	75	79	111	264	95	

tion." That this statement is not warranted by experiment is evident from the tables cited and figures shown above: where it is shown clearly that under suitable conditions of measurement, the venous and fluid pressures run a remarkably parallel course. They vary in the same direction too often to be independent of each other. Modifying the venous pressure changes the fluid pressure in the same direction. It is clear from these facts that one of the factors determining the fluid pressure in the animal is the venous pressure in the skull. If the pressure

varies in the experimental animal under the influence of changes in the venous pressure, there is no reason for assuming that it does not do so in the intact animal.

In order to prove that the occlusion of the jugulars is not accompanied by the formation of an increased amount of fluid, the following experiment was carried out:

Small, black, male cur dog, weight 11 kilos. Animal prepared by the usual method as described above. Ether by constant insufflation. With all the pressures constant 1 cc. of NaCl was injected into the dural canal. The arterial pressure was unchanged at 124 mm., venous pressure was *unchanged* at 144 mm., fluid pressure *rose* from 120 mm. to 230 mm., as recorded by our 1 mm. manometer tube. The time required for a return approximately to the normal was *6 minutes* and the point reached was 126 mm. After the return of the pressure to the normal, the fluid pressure was raised to the same degree by ligation of the veins. In this case *both venous and fluid pressure rose*, the former from 146 to 250 mm., the latter from 126 to 225 mm. Release of the veins was followed by a rapid return of both pressures to the normal levels, in *11 seconds*.

This experiment, fully substantiated by numerous others, shows conclusively that the time required to reduce the fluid pressure by the absorption of a sufficient amount of fluid necessary to produce a rise of about 120 mm. in the fluid pressure is enormously longer—about thirty-three times as long—than the time required to reduce an equal increase in the fluid pressure produced by ligation of the veins. Further, the former rise is accompanied by *no change* in the venous pressure, the latter is accompanied by *an increase* in the venous pressure. For these reasons it is perfectly clear that the rises in the two cases must be due to fundamentally different causes. Since in the first experiment, where we *know* there was an increase in the fluid 6 minutes were required for readjustment, while the last experiment where the pressure rose to the same degree required only 11 seconds for readjustment, where new formation was assumed but not proved, we believe that we are justified in stating that ligation of the jugulars does not cause "increased production of fluid," nor so far as our experiments are concerned is there any evidence whatever that there is delayed absorption of fluid. If any increase in the fluid in the canal resulted from the ligation of the veins, a longer period than 11 seconds would be required for readjustment after the release of the veins, for a longer period is required where the fluid is introduced by means of a hypodermic. This rapid readjustment can be seen graphically recorded in figure 3.

The third explanation that the rise in pressure is simultaneous but independent is possible but improbable in the highest degree.

Table 7 establishes the following facts: The ligation of the jugulars—taking an average of eighteen experiments—raises the venous pressure 139.6 mm., the fluid pressure 86.5 mm. Releasing the jugulars lowers the venous pressure 124.0 mm., the fluid pressure 86.7 mm. The changes in the venous and fluid pressures are synchronous both in a positive and a negative direction. As will be noted, both pressures returned approximately to the starting point immediately after the veins were released, a point of theoretical importance.

The conclusions we draw are the following: Raising the venous pressure raises the fluid pressure, lowering the venous pressure lowers the fluid pressure. The changes are not equal, but are more nearly equal in our experiments than in those reported by our predecessors, and we believe they would be almost exactly equal if a perfect method for measuring were devised, one by which the measurement is taken without withdrawing fluid from, or adding fluid to the canal. The measurement of venous pressure is absolutely necessary in order to rule out mechanical changes due to changes in venous pressure.

4. The influence on the venous pressure of altering the cerebrospinal fluid pressure

In the last section it was shown that raising the venous pressure increases the fluid pressure, and lowering the venous pressure lowers the fluid pressure. Let us now consider what influence raising or lowering the fluid pressure has on the venous pressure. Our results are shown in table 8, and typical graphs in figures 6 and 7.

From the table and the figure it is evident that *increasing the cerebrospinal fluid pressure does not increase the venous pressure*, so long as the rise in the fluid pressure does not produce a rise in the arterial pressure. If the rise in the fluid pressure is sufficient to produce a rise in the arterial pressure, then the venous pressure may rise with it, as in figure 6, but such is not always the case. (See fig. 7). These results are exactly contrary to those reported by Dixon and Halliburton. In figure 9 (p. 139) these authors show a marked rise in venous pressure on raising the fluid pressure by 100 mm. of saline. That these authors do not find such a rise in venous pressure consistently is evident from their own tracings: Compare figure 9 (p. 139) with figure 15 (p. 147). In the latter experiment the rise in the fluid pressure was from 60 to 160 mm. —exactly 100 mm. rise—as in the other experiment, but the rise here was accompanied in the early period by no effect on the venous pres-

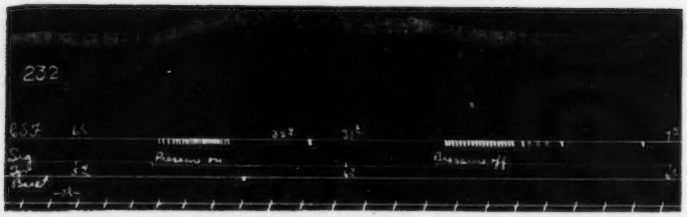

Fig. 6. This figure shows the effect on torcular venous and arterial pressures of raising the cerebrospinal pressure by 263 mm. of sodium chloride solution (from 61 to 324). Note that the arterial pressure rose slightly, and venous pressure rose slightly (13 mm.), as is to be expected under the slight rise in the arterial pressure.

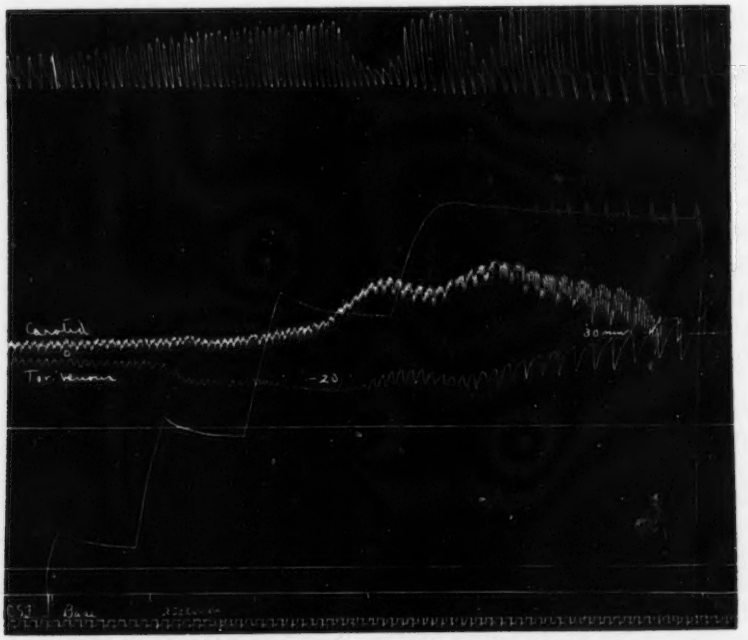

Fig. 7. This figure shows the results upon arterial and torcular venous pressure of increasing the fluid pressure. The pressure of the fluid is recorded graphically in millimeters of mercury. It is to be noted that at no time was the cerebral venous pressure increased. Note also that as the fluid pressure approaches that of the artery, the cardiac oscillations become more marked upon the curve traced by the fluid manometer.

sure, other than one synchronous with, and in the direction to be expected from a change in the arterial pressure. If their observations regarding the influence of the fluid pressure upon the venous pressure were correct the venous pressure should have risen markedly *early* in the experiment at the time the fluid pressure rose, but venous pressure did not rise. The same criticism holds to a less degree for the experiment shown in figure 14 (p. 146). The fact that the rise in the fluid pressure was produced by different means in the different experiments does not alter the results, to be expected from such a rise in the fluid

TABLE 9

Effects on the various pressures of the withdrawal of blood and its reinjection. Hemorrhage and transfusion

TRACING	AMOUNT WITHDRAWN AND REINJECTED	ARTERIAL			CIRCLE OF WILLIS			TORCULAR			CEREBROSPINAL FLUID		
		B	D	A	B	D	A	B	D	A	B	D	A
	cc.												
159a	100	118	64	104	90	52	78	356	171	364	112	49	122
159b	100	102	52	70	76	44	52	363	236	229	122	45	91
163	100	128	104	128				53	16	42	18	−16	6
164	100	132	84	140				60	32	56	15	6	20
165a	100	120	76	110				40	9	38	6	−23	0
165b	100	120	64	106				66	65	64	100	3	112
166	100	120	82	126				72	18	57	36	−12	20
174a	100	108	80	112	72	62	74	205	138	202	98	65	108
175b	100	114	90	118				208	168	205	110	75	116
205	100	152	132	158				146	123	138	97	78	108
206	100	154	130	156				138	126	133	104	76	107
207	200	146	104	144	90	72	94	138	110	146	97	49	103
Averages		126.1	88.5	122.6	82	57.5	74.5	153.7	101.0	139.5	76.2	32.9	76.1

pressure, for in our opinion the rise cannot be due to anything other than a mechanical change, and even if the fluid were increased, if their conclusions are correct increased fluid pressure must raise the venous pressure at the same time.

In the experiment cited in table 9 it is to be noticed that no rise such as they report as the usual result ever appeared. This is true whether the pressure be applied at the fourth ventricle through a second needle inserted near the trocar through which the fluid pressure is measured, or in the parietal region through a tube screwed into the skull, after

trephining and incising the dura. In no case did the venous pressure change to any degree under the influence of moderate increase in fluid, unless there was a synchronous and parallel change in the arterial pressure in amount sufficient and in direction correct to account for the venous pressure change. Further, it was noted in experiments performed for another phase of the problem that injections made into the third ventricle by transcallosal puncture raised the fluid, but not the venous pressure. We noted the increase in the venous pressure on increasing the fluid pressure in one animal only, and in that animal a post-mortem examination revealed a communication between the sinus at the torcula and the subarachnoid space, with blood in the fluid. In this case injection either in the parietal region or into the fourth ventricle increased the pressure in the vein. From these facts we are forced to the conclusion that figure 9 shown in Dixon and Halliburton's work may have been made upon an animal with such a communication between the sinus and the subarachnoid space. In our nineteen experiments made on six dogs, where no communication existed *increasing the cerebrospinal fluid pressure DID NOT increase the venous pressure in the sinus.* In four experiments on one animal, where such a communication existed, raising the fluid pressure raised the venous pressure, but not to the same degree as the fluid pressure. This is proof for the statement made earlier in the paper, that the fact that the venous and fluid pressures were not the same is no proof that no communication between the sinus and subarachnoid exists.

A careful consideration of the structures within the skull and of their arrangement would warrant the above findings. The pressure of the venous blood lying within the flexible sinuses must of necessity exert much influence upon the fluid, if the latter surrounds the sinuses in normal amounts. On the other hand the fluid cannot exert much influence upon the venous pressure, for as soon as the pressure in the subarachnoid space increases appreciably above that in the venous sinuses, the latter will collapse, forcing the blood onward toward the heart. Any further increase in the pressure will then be exerted upon the skull, not upon the venous blood in the sinuses.

The use of higher pressures always results in alteration of the arterial pressure and a change in the venous pressure, sometimes raising, sometimes lowering it.

Lowering the fluid pressure by drainage does not affect the venous pressure. If lowering the fluid pressure lowers the venous pressure, and a normal venous pressure is necessary for the normal formation of

the fluid, then none of the experiments reported by Dixon and Halliburton in their first paper can be correct, for they used the outflow method for estimating the influence of extracts of the choroid and other substances upon the fluid, a method which reduced the fluid pressure, and if they are correct must have reduced the venous pressure. The same criticism holds for all experiments in which the outflow method was employed. However, reducing the fluid pressure does not reduce the venous pressure in the torcula.

The conclusions we have reached are the following: Raising the fluid pressure by moderate amounts (100 to 200 mm. of NaCl solutions sp. gr. 1088) *does not* affect the venous pressure unless the arterial pressure is affected. Lowering the fluid pressure does not affect the venous pressure. The conclusions of Dixon and Halliburton are not in keeping with our results, and may have been based on observations on an animal with a communication between the sinus and the subarachnoid space. As shown in table 9, in nineteen experiments on six animals in which no such communication existed as proved by the post mortem, raising the pressure moderately produced no rise in the venous pressure. In four experiments where such a rise was seen, a communication between the sinus and the subarachnoid space was found at autopsy. We are dealing here with a question of fact, and confirmatory evidence from other workers is needed. However, we are sure that evidence in support of our own results will be forthcoming.

In figure 7 we show an experiment where higher pressures were used. The pressures in this case are recorded in millimeters of mercury and the venous pressure fell. This gives purely objective proof that Dixon and Halliburton (p. 139), are wrong in their conclusion that "Such a rise (in C. S. pressure) always produces a passive increase in cerebral venous pressure." This experiment gives the facts for low as well as high pressures. This same tracing gives the proof also that Frazier and Peet (p. 272) are incorrect, at least so far as cardiac oscillations are concerned, in their statement: "Sufficient intracranial pressure can easily be made to arrest these respiratory and cardiac oscillations. . . . . When a column of water was introduced under pressure only slightly in excess of the venous pressure the oscillations were arrested." That Frazier and Peet are not correct is brought out clearly in our graph. The oscillations in the mercury manometer become more nearly equal to those of the blood pressure manometer, the nearer the pressure in the subdural space approaches the intravascular diastolic arterial pressure. This is exactly what is to be

expected, for the skull, brain and the intracranial blood vessels reproduce almost exactly the conditions obtaining in the arm band of the blood pressure machine when the diastolic blood pressure is being measured. The undilatable cranium represents the arm band, the brain the muscles of the arm, and the layer of blood vessels the pulsating brachial artery. If the oscillations in the air of the expanded arm band increase the more nearly the pressure in the band approaches that of the blood vessel, then the oscillations of the fluid must increase the more nearly the pressure equals that of the diastole in the pulsating vessels.

Since venous pressure can be shown to affect the fluid pressure directly, and since the fluid pressure can be shown not to affect the venous pressure directly, it follows that all other factors remaining constant, e.g., the arterial pressure, secretory pressure, etc., then if both venous and fluid pressures rise at the same time, then the rise in the venous pressure caused the rise in the fluid pressure, and not the rise in the fluid pressure the rise in the venous pressure, it is theoretically possible, then, if secretagogues for the fluid exist, to increase the volume of the fluid in the canal by the action of the substance of the secreting cells to such a degree as to produce a rise in the fluid pressure independent of a rise in the arterial and venous pressures, a change which would be impossible if Dixon and Halliburton were correct, for as the fluid pressure rose it would force the venous pressure to rise with it. Further comment on this phase will follow later under the action of drugs.

5. The effects of altering both arterial and venous pressures in the same direction

Having studied the effects of alterations in venous and fluid pressures with little change in the arterial pressure, it becomes necessary to study the effects on the fluid pressure of alteration in the arterial and venous pressures when these vary in the same direction. We will study first the effect of reducing these pressures.

Literature: On this point we find only the work of Dixon and Halliburton (12) who summarize (p. 142) their observations as follows: "If the arterial and venous pressures are lowered, as for example by bleeding, the drop in C. S. pressure is relatively small."

Experimental: a. Hemorrhage and transfusion. We carefully repeated these experiments with the modification that the blood was drawn

from the femoral artery into a large pipette and re-injected into the femoral vein before coagulation could occur. Table 9 shows the results of twelve such experiments. As may be seen from the averages, all three pressures fall on the withdrawal and rise after the restoration of blood. As may be seen from figure 8, the fall in all the pressures is synchronous, as is also the rise. The readjustments are good: all the pressures remain on the average a little higher than they were originally. There is every reason for believing the change here to be of a purely mechanical nature, for there is no apparent reason for thinking them to be anything else. By no conceivable way can we see how hemorrhage and transfusion could have any but a purely mechanical effect by way of the vascular system. As will be seen from our experi-

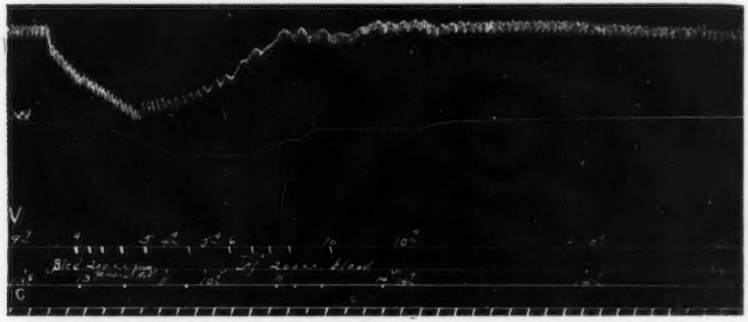

Fig. 8. This figure shows the effect of the withdrawal of 200 cc. of blood from the femoral artery, and its reinjection into the femoral vein.

ments, the average fall in torcular venous pressure was 52.7 mm., in fluid 43.3 mm., showing the fluid pressure fall to be 80 per cent of the fall in the venous pressure. This is much greater proportionally than the amount of fall noted by Dixon and Halliburton, who in a single experiment recorded show a fall in the fluid of exactly 10 per cent of the fall in the venous pressure. In the graph they show (p. 133) the venous pressure fell from 380 to 230, a fall of 150 mm. of 10 per cent citrate; the fluid pressure fell from 160 to 135, a fall of 15 mm. 10 per cent citrate. The explanation of the marked fall in our experiments as compared with those in the experiments of Dixon and Halliburton is found, of course, in the discussion of the influence of manometers of various sizes. There we found that with a wide manometer tube,

with a falling venous pressure, the fluid pressure would always remain higher than would be the case in the intact animal from overfilling the canal by the excessive amount of fluid in the manometer.

The authors named did not perform the reverse of this experiment; viz., the re-injection of the blood. As can be seen from table 9, re-injection of the blood raises all three pressures well up toward the original levels. Arterial pressure rises from 88.6 to 122.6; venous pressure rises from 101.0 to 139.5; and fluid pressure rises from 32.9 to 76.1. In this case in the average of twelve experiments the fluid rise is 110 per

TABLE 10

Effect of ligation of arteries entering the circle of Willis

TRACING	VESSEL	ARTERIAL			CIRCLE OF WILLIS			TORCULAR			CEREBROSPINAL FLUID		
		B	D	A	B	D	A	B	D	A	B	D	A
177	Right	108	92	118				145	69	139	46	25	54
178a	caro-	112	124	114				142	101	138	52	25	66
178b	tid	112	80	120				138	110	148	64	5	82
279d		164	160	160				102	84	101	157	140	157
Average		124	114	128				131.7	91.0	131.5	79.7	51.2	89.7
179	Carotid	114	112	118				216	146	206	87	57	90
181c	and	118	70	120				235	215	243	85	53	66
181d	verte-	124	90	124				202	208	235	64	81	80
201	brals	150	174	146	98	30	84	142	65	146	99	1	97
202		146	168	146	88	40	84	137	78	128	88	13	85
203		148	164	146	84	40	88	128	83	136	85	16	93
204		148	174	156	88	36	80	134	79	161	89	23	115
173b		134	160	142				74	58	72	42	21	24
Average		135.2	139.0	137.2	89.5	36.5	84.0	158.5	116.5	165.9	79.9	33.1	81.2

cent of the rise in venous pressure. This excessive rise is due undoubtedly to the piling up of fluid in the medullary region. It is evident that lowering venous and arterial pressure is accompanied by a proportional fall in the fluid pressure.

b. Ligation of the vessels to the head. Another easy way of producing decreased arterial pressure in the skull without much effect upon the general arterial pressure is to ligate the arteries forming the circle of Willis. As has been shown by Hill, ligation of the vertebrals and the carotids is not followed in the dog by an anemia sufficient to produce death, because of the anastomosis of the arteries of the trunk with

those of the spinal cord. Thus sufficient blood supply to the brain is afforded to support life. Experiments on this point are shown in table 10 and in figure 9.

As may be seen by the study of these reports, ligation of one or more of the three remaining arteries entering the circle of Willis (the left carotid being used for the blood pressure) is accompanied by a fall in the arterial, venous and cerebrospinal fluid pressures in the head, and a rise in the general arterial pressure.

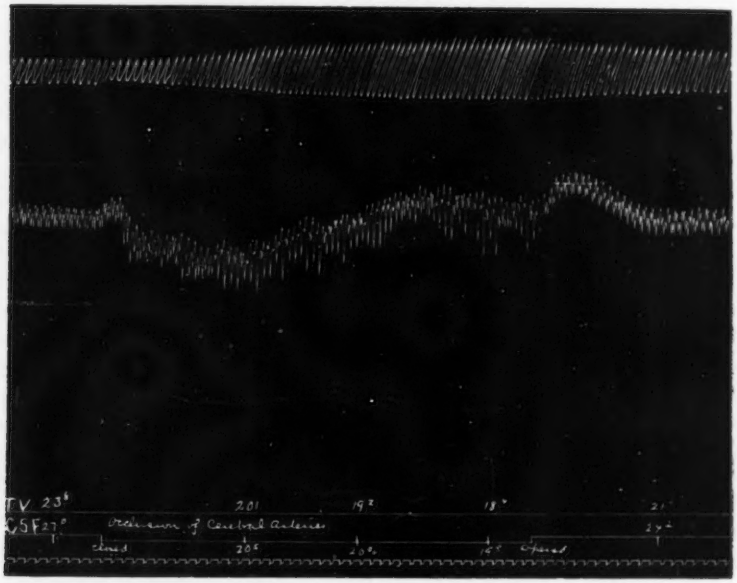

Fig. 9. This figure shows the effect on all the pressures of ligation of the arteries entering the circle of Willis.

In the manometer experiments ligation of the remaining carotid (right) produces an average fall of venous pressure of 41.7 mm. of sodium carbonate (1088), an average fall of fluid pressure of 31 mm. NaCl (1088), and an average fall of 8 mm. of mercury in the general arterial pressure. Ligation of the remaining carotid and both vertebrals resulted in an average fall in venous pressure of 42.0 mm., an average fall in fluid pressure amounting to 46.8 mm., a rise in general arterial pressure of 3.8 mm. of mercury, and a fall in the intracranial

arterial pressure of 53.0 mm. of mercury. Release of the carotid artery produced an average rise of 42 mm. in the venous pressure, of 38.5 mm. in the fluid pressure, and of 12 mm. Hg. in arterial pressure. Release of the carotid and vertebrals caused a rise of 47.5 mm. in the venous pressure, of 49.4 mm. in the fluid pressure, and a fall of 1.8 mm. in arterial pressure. These experiments clearly establish the fact that decreasing the arterial pressure to the brain decreases both venous and fluid pressures in the skull. Raising the arterial pressure raises the venous and fluid pressures in the skull. There is absolutely no reason for believing that the effects of the brief ligations are anything other than the effects of alterations in the arterial and venous pressures in the skull, reflected upon the fluid pressure. Experiments of this type do not give any evidence regarding new formation of the fluid although other writers have drawn different conclusions. A comparison of the pressure before and after ligation of the arteries shows an almost perfect readjustment to the original levels, a fact that speaks for mechanical alterations and readjustments. Only a few experiments of long duration were carried out. We have one in which the ligation of the carotid and vertebrals was maintained for 63 minutes. Pressure in the vein and fluid as well as in the circle of Willis remained low during the occlusion, and the general arterial pressure fell. On release the pressures all reached their original levels, except for the general arterial pressure, which remained low. We conclude, then, that ligation of the cerebral vessels produces only passive changes in the skull, characterized by a fall in the arterial, venous and fluid pressures in the cranial cavity, with an almost perfect readjustment when the vessels are released. This gives no evidence regarding the formation of the fluid, and does not give conclusive evidence that arterial pressure influences fluid pressure directly, for venous pressure fell simultaneously with the fall in arterial pressure.

c. Ligation of the various trunk arteries. We studied the effects of ligation of various arteries of the trunk on the fluid pressure, in an attempt to raise the blood pressure in the cranium above the normal by mechanical means. In both sets of experiments just cited, we are dealing with pressure falling below and then rising to the normal. As is so often the case in experiments of this kind, arterial pressure did not rise to any marked degree and hence the changes in other pressures are small. (See table 11, which shows the results of five such ligations. See also fig. 10).

As is apparent from the data in table 12, occlusion of the aorta or of the aorta and subclavians produces a slight rise in the arterial pressure accompanied by a slight rise in the venous and the fluid pressures. Release of these arteries produces a return of the pressures to almost exactly the original levels. These changes are purely mechanical: there is absolutely no reason for assuming either an increase or a decrease in fluid formation in such manipulation, the readjustments are almost perfect, and the changes are synchronous with and in the direction to be expected from the direction of the change in arterial pressure.

d. Adrenalin. A much more effective way of producing a rise in the arterial and venous pressure in the skull is the intravenous injection

TABLE 11

Effect of ligation and release of branches of the arterial tree

TRACING	VESSEL LIGATED	ARTERIAL			TORCULAR			CEREBROSPINAL FLUID		
		B	D	A	B	D	A	B	D	A
171b	Occlusion of aorta	138	132	140	83	75	68	50	46	47
172	Occlusion of aorta and subclavians	132	128	138	93	130	100	56	78	72
173a	Occlusion of aorta and subclavians	132	132	134	70	109	75	46	66	45
176a	Occlusion of aorta and subclavians	118	128	118	166	175	162	79	89	79
b	Occlusion of aorta and subclavians	116	124	110	164	170	156	62	68	53
Average		127.2	128.8	128.0	115.2	131.8	112.2	58.6	69.4	59.2

of adrenalin. This is especially true if the animal has been vagotomized or atropinized before the adrenalin is injected. When the blood pressure is raised by adrenalin there comes a synchronous rise in both venous and cerebrospinal fluid pressures. These rises in pressure, particularly that in the torcula, are so absolutely synchronous with the change in arterial pressure, that the conclusion that the rise in arterial pressure is the cause of the rise in the other pressures is inevitable. There is, as has already been stated, a tendency for the fluid pressure change to lag behind the arterial and venous change, so there comes a time, immediately after the end of the arterial and venous rise, when the arterial and venous pressures are stationary or falling at a time when the fluid pressure is still rising. This fact may seem to be

hard to correlate with the statement made above that the arterial and venous rise is the cause of the fluid pressure rise. Matters become clear, however, when the various straits in the fluid pathway are considered. The resistance offered by these straits slows the adjustment of the fluid to such a degree that the fluid pressure never records its true maximum for two reasons: first, the pressure recorded is the true fluid pressure minus the amount lost by the fall in arterial and venous pressures; second, to this error must be added the error of pressure lost due to the draining of a certain amount of fluid from

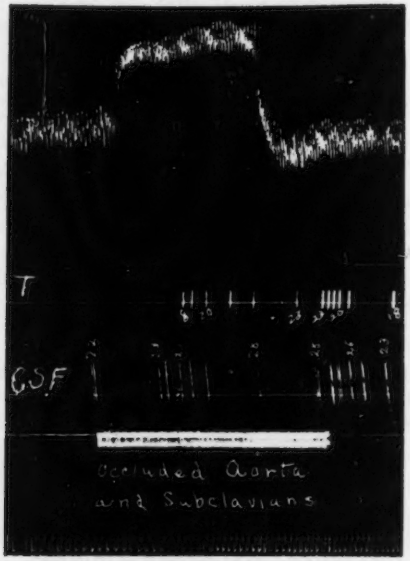

Fig. 10. This figure shows the effect on arterial, venous and fluid pressure of temporary ligation of the aorta and subclavians.

the canal into the manometer. The amount of this second error is modified by the bore of the manometer tube; it is large with a tube of wide bore and small with a tube of narrow bore. These two errors are always present and modify results to a considerable degree. Thus we are certain that if true fluid pressures were secured the pressure in the canal is considerably larger than those we record in our tables. In table 12 we record the results from eleven experiments. Many more were performed, but these show conclusively the results secured on this phase of the subject. (See fig. 11).

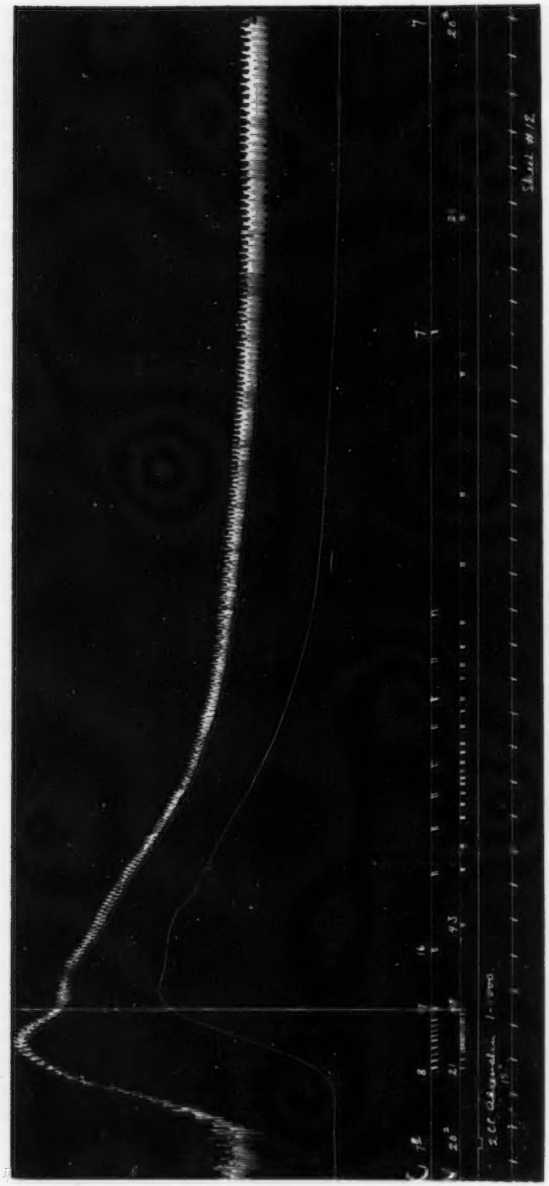

Fig. 11. This figure shows the effect on all of the pressures of raising the blood pressure by the intravenous injection of adrenalin. Note that fluid pressure, *C*, continued to rise an instant after venous pressure, *V*, had become stationary. Both venous and fluid pressures were still rising while arterial pressure was falling. Note that the readjustment is rapid and almost perfect. Compare this figure with figure 12 made on the same animal but after ligation of the jugulars.

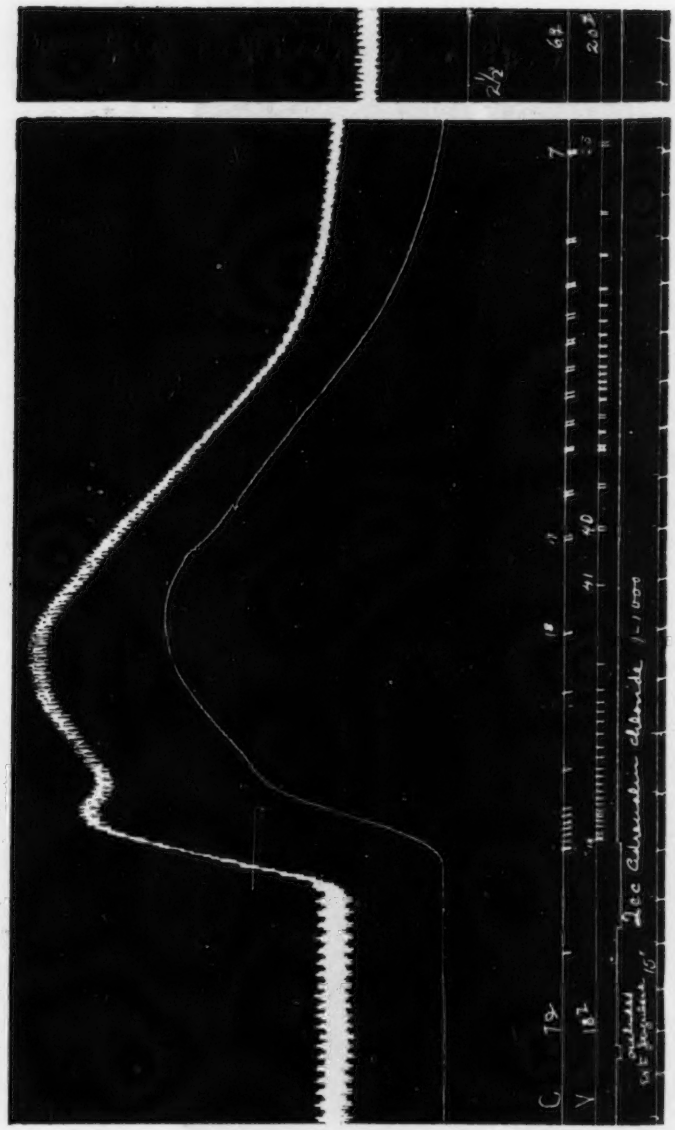

Fig. 12. From the same animal as figure 11, and made immediately after 11. The jugulars were ligated and adrenalin was administered intravenously. Note that all the pressures are practically the same as those shown in figure 11. In this case ligation of the jugulars produced no rise in the venous and fluid pressures.

It may be assumed that the rise and fall in venous and fluid pressure *may* be due to something other than the rise and fall in arterial pressure. For example, if the fluid should accumulate rapidly in the animal with the cranium intact as Spina observed in the animal with the calvarium removed—the rise in fluid pressure might be due to increased transudation. Then, if Dixon and Halliburton are correct in their contention that raising the fluid pressure raises the venous pressure, this increase in fluid pressure would produce an increase in venous pressure, which would persist until the fluid was absorbed—a process taking place, according to all modern workers, along the venous channels. Ligation of the jugulars must then produce ideal condition for transudation for it would increase capillary pressure and this would be markedly augmented by the action of adrenalin forcing the arterial pressure to a high level. The fluid then being formed could not be absorbed because of the failure of outflow of blood through the jugulars; and thus if Dixon and Halliburton are correct in their contention, the fall of fluid and venous pressure would of necessity be delayed in the case where the jugular is ligated. (See fig. 12). Comparison of the two figures, 11 and 12, shows that allowing for difference in the arterial curves, the return to normal is as rapid in the case where the jugular is ligated as in the case with the jugular open.

From the data shown in table 12 it is evident that a rise in arterial pressure caused by adrenalin is accompanied by an enormous rise in the venous and fluid pressures inside the skull. This venous pressure rise is absolutely synchronous with the arterial rise, the fluid rise lags slightly behind arterial and venous rise, due undoubtedly to the slowing of the adjustment between pressures inside and outside the skull, by straits in the system, particularly at the needle and at the aqueduct of Sylvius. There is no doubt in the mind of the writer that the venous rise is the result of the rise in arterial pressure, produced by the high arterial pressure exerted directly upon the intracranial structures, forcing the blood through the capillaries of the brain, thus raising the torcular pressure. Since the animal has been atropinized, there is no cardio-inhibition. The fluid rise is 60 per cent of the venous rise. We know from experiments cited earlier that a rise in venous pressure produces a rise in the fluid pressure, and that a rise in fluid pressure by itself produces no change in venous pressure, therefore it seems most probable that the rise in venous pressure is the cause of at least part of the rise in the fluid pressure. What has just been said regarding the rise in pressures applies equally well to the fall in the various

pressures, and it is thus obvious that a rise in the arterial and venous pressures produces a rise in fluid pressure, a fall in these pressures produces a fall in the fluid pressure.

The rise and fall in arterial pressure adequately explains all the changes in venous and fluid pressures because the rise and fall in all pressures are synchronous if we allow time for the venous and fluid pressures to adjust themselves in their complicated systems. There is evidence against rapid new formation and absorption of fluid with a synchronous rise in venous pressure due to increased fluid pressure under the influence of adrenalin. For while new formation might explain the rapid rise, and reabsorption the rapid fall, the latter assumption is disproved by the fact that the readjustment is not delayed by ligation of the jugulars, nor is the curve following the administration of adrenalin materially changed by such a ligation.

TABLE 12

The effect of adrenalin after atropine on the various pressures

TRACING	ARTERIAL			TORCULAR			FLUID		
	B	D	A	B	D	A	B	D	A
39	110	238	106	17	48	16	15	30	9
114	98	190	86	202	430	202	78	170	70
115	98	212	86	187	410	204	70	180	69
117	88	176	44	13	42	13	3	15	3
212	108	222	94	124	281	129	86	199	89
216	130	262	126	55	262	56	113	270	94
219	52	196	50	24	144	23	27	116	26
221	126	272	120	181	418	185	91	191	76
222	130	194	110	275	402	251	104	160	114
238	96	254	94	149	397	150	120	315	121
239	84	236	80	135	406	139	105	291	104
Average.....	101.8	222.9	90.5	123.8	294.5	124.3	73.8	176.0	70.4

We therefore conclude that the administration of adrenalin produces purely passive changes in the arterial, venous and fluid pressures, although rapid outflow of fluid follows such an injection if the outflow method of study is employed. (See fig. 13). Most recent writers hold this view regarding the effect of adrenalin on fluid formation, our only contribution is additional proof.

e. Effect of raising arterial pressure, with the venous pressure remaining constant. Having shown the effect on fluid pressure of raising arterial

pressure under conditions where there was a simultaneous rise in venous pressure, it is now necessary to show the effect on the fluid pressure of raising the arterial pressure independent of a rise in the venous pressure. Accepting the view that the only effect that adrenalin has on the fluid is a mechanical one—a point which we believe to be proved satisfactorily—we injected this drug intravenously to raise the arterial pressure. In order to maintain the venous pressure constant, the reservoir cannula in the torcula was attached on one hand to the manom-

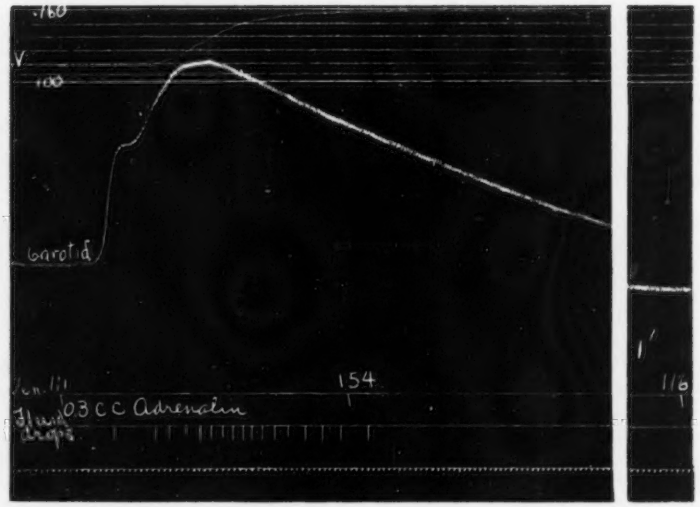

Fig. 13. This figure shows that if the outflow method is employed, the injection of adrenalin is followed by a marked rise in the torcular venous pressure, *V*, as well as in the arterial pressure, and a marked outflow of fluid. The outflow decreases on repeated injections.

eter, on the other to a short wide glass tube fastened in an upright position, and so adjusted that when the tube was full it exactly balanced the pressure in the sinus. Then when the venous pressure began to rise with the beginning of the adrenalin action, blood was forced over the end of the tube. In this way venous pressure was limited to that observed in the sinus at the beginning of the experiment. Some blood was lost by the animal during the experiment, but not enough materially to lower the blood pressure in the animal after the action

of the drug had ceased. Results from these experiments and a graph of one is seen in table 13 and in figure 14.

The results of the experiments recorded above, experiments carried out in four animals, show conclusively that if the venous pressure is maintained practically constant in the head by permitting the blood to escape from the sinus, and the arterial pressure is raised by the use of adrenalin, then the fluid pressure rises to almost the same degree as in the usual experiment, where the venous pressure rises with the arterial. From these experiments we conclude that arterial pressure,

TABLE 13

Effect on fluid pressure of raising arterial pressure with venous pressure kept constant

CONDITION	ARTERIAL			TORCULAR			CEREBROSPINAL FLUID			SUMMARY		
	B	D	A	B	D	A	B	D	A	Arterial rise	Venous rise	Fluid rise
Sinus closed	130	262	126	55	262	56	113	270	94	132	207	157
Sinus opened	126	254	108	59	69	59	97	226	71	128	10	129
Sinus closed	126	254	106	91	339	111	105	257	91	128	238	152
Sinus opened	124	250	110	73	95	57	95	206	85	126	22	111
Sinus closed	126	272	118	181	418	185	91	191	76	146	237	100
Sinus opened	122	270	114	175	205	180	82	218	83	148	32	136
Sinus closed	84	236	80	135	406	139	105	291	104	152	271	186
Sinus opened	78	226	94	129	129	129	102	279	101	148	0	177
Average sinus closed.....	116.5	256.0	107.5	115.5	356.2	122.7	103.5	252.2	91.2	139.5	238.2	148.7
Average sinus opened.....	112.5	250.0	106.5	109.0	124.5	106.2	94.0	232.2	85.0	137.5	16.0	138.2

if high, can and does influence the fluid pressure directly. A rise in the arterial pressure *can* produce a rise in the fluid pressure independent of a rise in the venous pressure. We would be more certain regarding these results if it were possible for us to take the venous pressure at some other point besides the point at which the fluid makes its escape, but to devise such a method seemed out of the question in the animals we were working with. An animal much larger than a dog would have to be employed. One observation made in some of these experiments is interesting: during the early pressor phase of adrenalin action the

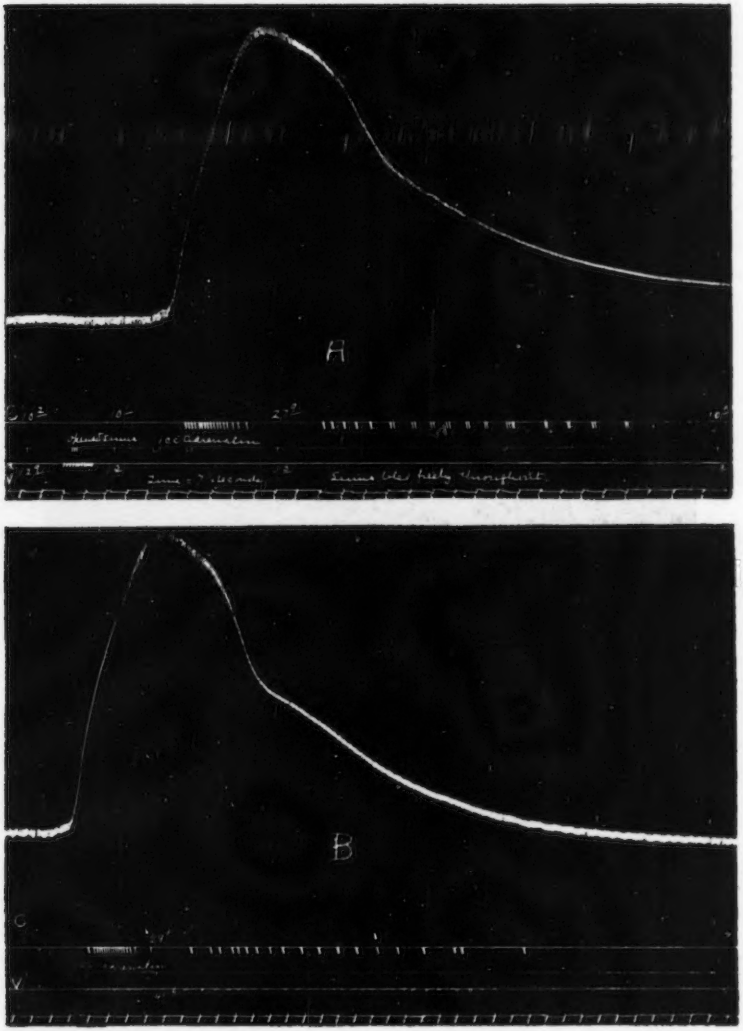

Fig. 14. This figure shows the marked similarity in the arterial and fluid curves no matter whether the sinus was open or closed. In *A*, the sinus was open and the fluid pressure rose from 101 to 279, the venous pressure remaining low on the injection of adrenalin. In *B*, the sinus was closed, the fluid pressure rose from 105 to 291, the venous rising from 135 to 406. For some reason the fluid pressure did not fall in *A* when the sinus was opened, as is usually the case (see fig. 5).

sinus bleeds freely, a considerable amount of blood flowing out over the end of the tube. Later, but before the pressure in the artery has reached its height, this outflow ceases. It is therefore evident that the source of blood for the sinus is cut off at the highest point in the blood pressure curve, probably by the obliteration of the capillaries by the high intracranial pressure. These experiments are contrary to the results reported by Howell. (See fig. 15, which proves that

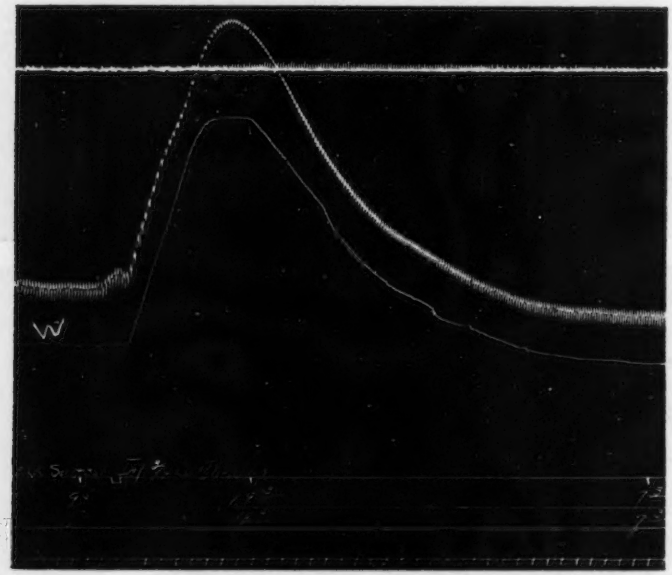

Fig. 15. This figure shows that in some instances the circle of Willis, *W*, is occluded during the action of adrenalin. This phenomenon was not frequently observed, in only about 2 per cent of cases.

parts of the circle of Willis are occluded during the height of the blood pressure rise with adrenalin).

From our experiments on the effects of venous pressure and of arterial pressure upon the fluid pressure it is evident that the pressure in the fluid is the result of the combined influence of at least two pressures—venous and arterial. Of these two the venous millimeter per millimeter is of much the greater importance, but under certain conditions the pressure of the fluid must be augmented by the arterial pressure. Under

these conditions the cerebrospinal fluid pressure is higher than the venous pressure in the torcula.

6. The influence of the peripheral vagus. The stimulation of the peripheral end of the vagus because of the profound effect it has upon the circulation and distribution of blood should have a marked effect upon the pressure of the cerebrospinal fluid.

Dixon and Halliburton (12) studied the effects of such stimulation and divided the results into three groups (p. 138):

> (1) When the fall of blood pressure is small a slight passive diminution of the c-s pressure without any subsequent rise, even though the torcular pressure rises greatly; (2) an initial passive fall in pressure followed by a rise, which commences whilst arterial and venous pressures are still low; (3) an immediate rise in c-s pressure which may be regarded as being caused by increased secretion due to deficient oxygenation or the collection of carbon dioxide in the brain.

In table 14 we record the results from nineteen stimulations of the peripheral vagus on fourteen animals. We show in figure 16 what we consider typical results. So far as the table is concerned, the average result is a marked fall in arterial pressure early in the stimulation, with a gradual but very slow rise in the pressure, this is followed by a sudden rise when stimulation ceases followed by a gradual rise to normal. Numerous variations are seen. Such a marked fall in arterial pressure might in the skull either raise or lower the venous pressure although in the general circulation it commonly raises it. Our measurements show a fall in venous followed during the stimulation by a rise almost to normal, with a fall later below the level reached after the early effects of stimulation has passed off. The curve of the fluid pressure is exactly similar.

In figure 14, *A* and *B*, it will be noted that all the pressures fell simultaneously and rose simultaneously. In *A* the fall in all pressures was great, and the recovery was to above normal. In *B* the fall was much less marked and the recovery was incomplete in all the pressures. *C* is given to show that in some experiments there is a rather marked fall in arterial pressure but very little change in venous or fluid pressure. The decrease in cardiac output in these cases apparently is almost exactly balanced by the venous engorgement so that the venous pressure remains almost a constant. There is a rather large percentage of such cases seen in experimentation. We have never seen results such as reported by Dixon and Halliburton in figure 8, where torcular venous pressure rose markedly without raising the fluid pressure.

TABLE 14

Effect of stimulation of peripheral vagus. This table shows the effect on arterial, venous and fluid pressure of stimulations of the peripheral vagus. On account of the nature of the response, two readings are recorded of the effect during and subsequent to the stimulation

TRACING NUMBER	GENERAL ARTERIAL					TORCULAR VENOUS					CEREBROSPINAL FLUID				
	B	D		A		B	D		A		B	D		A	
		1	2	1	2		1	2	1	2		1	2	1	2
167	132	100	102	108	122	99	90	79	80	120	116	100	110	110	149
175a	122	112	108	140	126	210	210	209	209	202	118	118	120	120	108
175b	124	114	128	128	128	176	176	176	176	176	91	91	91	94	87
183	144	128	128	154	154	69	70	80	78	70	115	105	100	115	115
184	148	116	116	140	168	116	100	150	111	118	96	80	93	80	86
185	166	116	140	154	164	109	100	117	116	114	85	85	86	85	83
186	156	130	132	140	160	113	109	113	115	121	83	83	83	83	84
187	164	140	162	162	158	121	121	123	123	125	86	86	91	91	91
258	180	158	162	166	180	119	110	116	116	116	150	140	145	145	137
259a	180	160	162	176	180	143	140	131	130	102	137	137	134	130	90
259b	180	32	32	124	170	102	100	109	110	103	90	90	118	120	106
260a	180	170	174	184	182	110	111	164	160	124	101	110	155	150	102
260b	184	176	176	186	184	123	123	141	140	141	102	102	102	102	109
260c	188	164	170	190	186	141	140	101	101	109	99	99	99	98	104
261a	176	70	60	168	168	108	100	100	100	100	104	100	100	100	120
261b	124	30	30	146	154	75	70	90	120	106	77	80	100	110	99
262a	148	32	32	132	164	101	100	90	90	97	107	102	102	102	120
263	150	126	128	142	142	169	160	145	145	136	191	190	158	160	162
264	130	112	120	122	128	117	117	88	88	92	107	107	85	85	94
Average	156.6	115.0	119.0	150.6	158.8	124.7	118.3	122.2	121.4	119.5	108.1	105.5	109.0	109.4	107.7

1 = Records early change during and after stimulation.
2 = Records late change during and after stimulation.

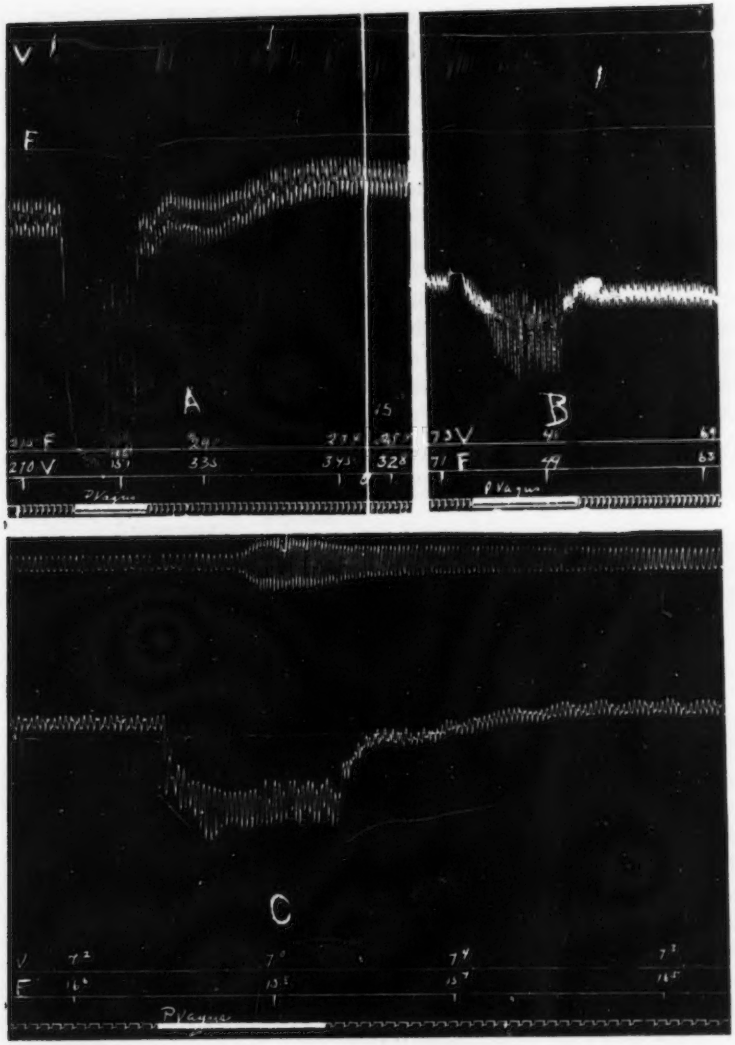

Fig. 16. This figure shows the effect on all the pressures of stimulation of the peripheral end of the cut vagus nerve. Note the marked differences in the changes of pressures in the different experiments.

Nor have we ever seen the result shown in figure 7, where arterial and venous pressure fell, but fluid pressure rose. We have no suggestions to offer as to the explanation of their results nor of our failure to observe similar ones.

So far as our experiments are concerned we are justified in the conclusion that the results of stimulation of the vagus upon the fluid pressure are exactly what are to be expected, if the changes are due to vascular changes in the skull. There is no evidence of new formation under the influence of the partial asphyxia produced.

7. Influence of the amount of fluid in the canal. One of the factors which influences the effect of a rise of the fluid or of an increase in the venous or arterial pressures is the amount of fluid in the canal. Early in the work we noticed that in rather a large percentage of animals the response of the fluid pressure to venous and arterial changes was small.

TABLE 15

Dog, prepared as described above. Blood pressure raised by the intravenous injection of adrenalin

	ARTERIAL RISE	TORCULAR VENTRICULAR RISE	CEREBROSPINAL FLUID RISE	FLUID RISE / VENTRICULAR RISE
Normal	156	197	149	0.75
2 cc. fluid drawn	172	167	80	0.48
5 cc. salt injection	172	439	390	0.88
2 cc. fluid drawn	162	277	174	0.63

These records were marked "animal refractory to drugs" in our book. Later it was found that this refractory state could be changed to a non-refractory one by the introduction into the canal of a few cubic centimeters of warm salt solution. Similarly an animal which reacted well could be converted into a refractory one by the withdrawal of some of the fluid. The importance of this factor has already been brought out in the influence of the various bores of manometers on the rising and falling fluid pressure. In general the more fluid there is present in the canal the greater the response of the fluid to vascular changes. Many experiments were done to prove this point; there is some variation in the results but the statement made above holds, as may be seen from the following experiment (table 15):

As can be seen from this experiment the more fluid there is in the canal the more nearly does the rise of pressure in the fluid equal the rise in the pressure in the vein. The cause is so obvious as to need

no comment. It is an important factor in the response of the animal to the action of hemodynamic drugs, but one which has been neglected as is proved by the choice of method made by many of the workers in the field. The effect is a purely physical one. These experiments confirm also the statement made regarding the effect of the bore of the manometer tube upon the record of the fluid pressure, for it makes no difference whether the fluid is drawn out into a syringe or into a manometer tube, the effect on the pressure change is the same. We consider it highly probable that the amount of fluid varies within wide limits in different animals, hence the amount of response will vary widely, and many animals must be observed in order to get a reasonably accurate average. This fact explains why the fluid pressure was high even in those animals with an epidural hemorrhage in which case no blood entered the fluid, for it makes no difference whether the material is inside or outside the dura, so long as it lies within the bony calvarium, the result will be the same.

8. Effects of respiration

Among the physiological changes which *a priori* are likely to produce alterations in the fluid pressure or fluid outflow must be considered the effects of respiration, and in this connection not only must the effects produced by each individual respiration be considered, but also the effects of continued increased respiratory rate and depth. The oscillations produced in the fluid during each respiration are evident to anyone who will take the trouble to open the spinal canal of an animal under an anesthetic. As may be seen, in the ordinary case, with each inspiration the fluid falls, with each expiration, the fluid rises toward the hole in the wall of the canal.

Literature. The details of these changes have been carefully worked out by Knoll (26), and his observations can be fully substantiated. We do not believe that the criticism of Hill on this work is well taken, at least not for the experiments in which the loss of fluid from the canal is small. Previous to Knoll's work, Salathe (27) ascribed the pressure changes observed to take place during inspiration to the inspiratory rise in the blood pressure, while Haller and Fredricq (28) have ascribed the changes to alterations in the venous pressure occurring during the respiratory cycle. Knoll bases his conclusions that the pressure changes in the fluid are due to the changes in the venous pressure upon the following observations: *a*, The increase in the fluid pressure is not

exactly synchronous with the increase in the arterial pressure to the nervous system. *b*, The fluid pressure changes are modified but not lost by ligation of the arteries to the head, even when there was included the aorta close below the origin of the left subclavian artery. *c*, The pressure changes were synchronous with changes in the venous pressure, and in the same direction. *d*, One point against the venous origin of the pulsation in the fluid was the observation that ligation of the superior vena cava distal to the *vena azygos* and the inferior vena cava did not abolish the pulsation entirely. This he explained by the fact that in such a ligation the *vena azygos* is still open, and it is through this vein that the fluid pressure is still modified by changes in the venous pressure. This is rendered the more probable by the observation that in such conditions—ligation of the cavae—the small veins from the spinal plexus to the azygos system are markedly engorged with blood. He admits that in some cases the fluid may be so markedly influenced by the arterial pressure as to show an increased fluid pressure during inspiration and a decreased fluid pressure during expiration, a rhythm the reverse of the normal, but says that these cases are exceptional. This work of Knoll's has been carefully done, and is essentially correct, but he neglected to mention the influence on the pressure changes of alterations of the fluid volume in the canal,—this latter is an important one,—for unless there is a large volume of fluid in the canal, the arterial pressure can not change the fluid pressure directly and can modify it only indirectly by way of the venous pressure. The statements just made apply only to the changes occurring during a single respiratory cycle.

More recently Dixon and Halliburton (11) using the outflow method reached the conclusion that under artificial respiration "increased rate or larger thrust causes slower secretion, while decreased rate or smaller thrust, a faster secretion." They ascribe these changes to alterations in the CO_2 content of the blood. To the same causes they attribute at least in part the increased outflow following chloroform inhalations in the normally breathing animal, an experiment in which according to their observations there is an increase in the outflow of the fluid.

Experiments: Our own work covers only a small part of the field: only the increased respiration due to stimulation of a sensory nerve, like the sciatic, and decreased respiration due to stimulation of an afferent inhibitory nerve like the superior laryngeal, or the central vagus, in the normally breathing animal. The effects of artificial respiration will be covered in a later paper.

a. Increased respiration: The effects of increased respiration upon the fluid pressure may be seen by referring to table 16. Experiments 500a to 501c were done on a dog in which stimulation of the sciatic always produced a fall in the blood pressure together with a fall in the venous and the fluid pressures. Experiments 504a to 505d were done on dogs in which stimulation of the sciatic always produced a rise in the arterial pressure, along with a rise in the venous and the fluid pressures. These statements hold true for both these animals not only for averages but for every individual experiment. The remaining five experiments were done on one other dog in which, as can be seen, stimulation of the sciatic always produced a rise in the arterial pressure, while the effects on the other pressures varied to some degree. The averages of the eighteen stimulations are shown in the final averages given at the bottom of the table. The conclusions to be drawn from these experiments are the following: The arterial, venous and fluid pressures rise in those cases where the stimulation of the sciatic has a pressor effect, and fall in those cases where that nerve has a depressor effect. The changes as shown by our eighteen experiments are all to be accounted for by alterations in the vascular pressure in the skull, for the pressure in the fluid varies in the direction to be expected from the alterations in arterial and venous pressures inside the skull. The averages of change between dogs, some of which show pressor, others depressor effects on stimulation of the sciatic, are well within the range of experimental error, and hence it is entirely unnecessary to assume either an increase or a decrease in the rate of formation of the cerebrospinal fluid. (See fig. 17).

Table 17 shows the results of increased respiration upon the outflow of fluid from a needle inserted into the 4th ventricle. The value to be placed upon this form of experiment has already been discussed in detail in our criticism of the methods of the study employed. However, we doubted some of the statements of recent workers regarding the behavior of the fluid on increasing the respiration. As can be seen from the table, in only two cases was there a decrease in the flow on increasing the respiration actively by sensory stimulation although it must be said that in many cases observed on other points in which the outflow method was used on increasing the respiration the fluid retreated out of sight into the tube, and did not reappear for some time. In ten cases recorded there was an increase in the outflow on increasing the respiratory movements, in two cases the rate was unchanged, and in three cases in this series the change could not be observed because of

TABLE 16

The effects on the various pressures of increased respiration produced by stimulation of the sciatic nerve

TRACING	VASCULAR AND FLUID PRESSURES									RESPIRATION					
	Arterial			Venous			C. S. Fluid			Rate			Amplitude		
	B.	D.	A.	B.	D.	A.	B.	D.	A.	B.	D.	A.	B.	D.	A.
500 a	176	150	176	215	201	209	215	202	208	40	76	44	8	41	8
500 b	176	156	174	209	199	207	208	197	207	48	76	40	8	40	8
500 c	174	158	176	208	200	207	207	197	203	40	76	40	8	38	8
501 a	168	154	176	201	198	206	201	194	208	33	60	34	7	31	7
501 b	176	166	180	207	202	208	204	201	207	34	60	37	7	31	7
501 c	180	160	176	208	201	207	208	199	206	37	68	37	7	38	7
Average	175.0	157.3	176.3	208.0	200.1	207.3	207.1	198.3	206.4	38.6	69.3	38.6	7.5	36.4	7.5
504 a	150	176	160	87	100	99	140	140	144	62	70	64	10	14	8
504 b	160	186	176	106	112	108	145	149	146	64	76	64	8	15	8
504 c	170	190	180	111	111	101	149	141	132	64	84	64	7	25	8
505 a	174	196	184	111	115	109	140	146	131	64	96	64	6	27	8
505 b	184	202	180	110	131	118	131	136	123	64	88	64	6	25	6
505 c	160	204	188	118	141	120	123	137	125	64	92	72	6	27	8
505 d	188	208	194	123	135	139	129	164	164	72	84	72	6	25	6
Average	169.4	194.5	180.2	109.4	120.7	113.4	136.7	144.7	137.8	64.8	84.2	66.2	7.0	22.5	7.4
300 a	128	130	124	165	175	168	131	123	117	42	58	41	7	16	8
300 b	130	144	128	168	177	152	118	115	109	44	59	43	8	17	7
300 c	132	152	130	152	168	151	107	107	106	40	57	38	9	18	8
300 d	130	140	130	157	169	149	106	110	104	46	58	44	8	16	8
300 e	128	146	134	149	155	136	104	105	107	41	49	41	8	14	9
Average	129.6	142.4	129.2	158.2	168.8	151.2	113.2	112.0	108.6	42.6	56.2	41.4	8.0	16.2	8.0
Average of all expers.	158	164.7	161.9	158.5	163.2	157.3	152.3	151.6	150.9	48.6	69.9	48.7	7.3	25.0	7.6

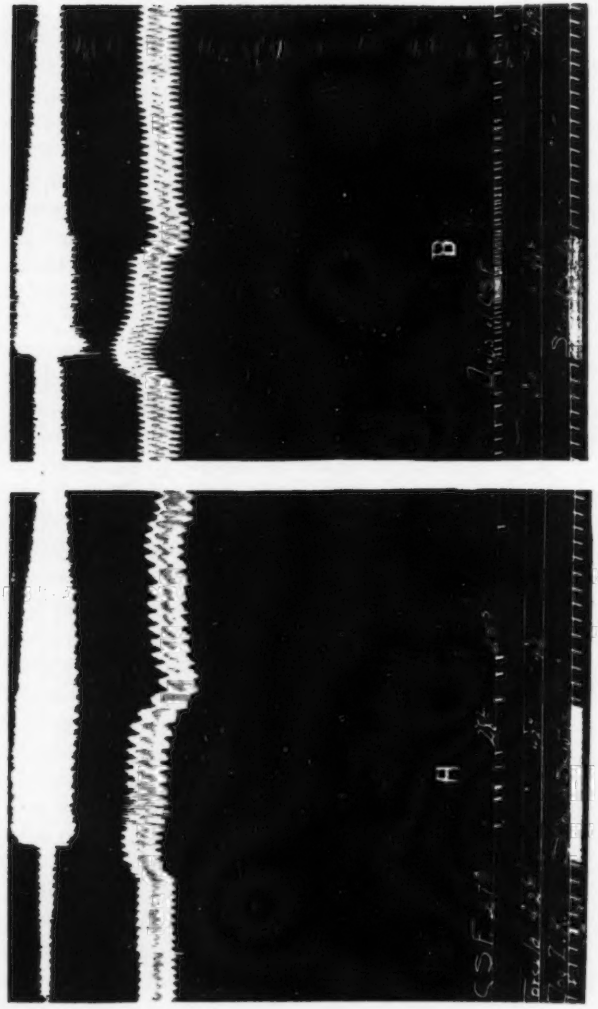

Fig. 17. This figure shows two experiments on the same animal: *A* is by the manometer, *B*, by the outflow method. Note that stimulation of the sciatic in *A* shows very little alteration in either fluid or venous pressure, while the same stimulation in *B* produces no marked change in venous pressure but a marked increase in the rate of outflow of fluid.

TABLE 17

Effect on the arterial and venous pressures and on the fluid outflow of increasing the respiration by stimulation of the sciatic nerve

TRACING	VASCULAR PRESSURES AND FLUID RATE									RESPIRATION					
	Arterial			Venous			C. S. Fluid in drops per minute			Rate			Amplitude		
	B.	D.	A.	B.	D.	A.	B.	D.	A.	B.	D.	A.	B.	D.	A.
502 a	182	160	190	181	178	199	†5.4	3.3	2.7	38	60	38	9	30	9
502 b	190	164	176	195	180	188	‡1.2	3.3	0.9	40	72	44	11	38	11
503 a	174	130	182	169	155	167	‡2.0	2.1	1.9	33	64	33	7	46	7
503 b	184	180	180	171	155	179	†1.9	1.5	2.0	32	68	40	11	43	7
257 b	194	202	192	412	426	419	8.0	35.0	10.1	38	45	39	6	16	7
256 a	198	192	190	382	406	398	1.0	17.6	11.1	40	46	39	6	18	7
256 b	188	196	188	392	375	379	2.0	21.3	12.0	38	44	39	7	15	6
255 a	190	194	190	299	319	342	20.0	29.2	15.0	48	58	46	5	12	10
255 b	190	194	188	261	363	359	2.0	13.3	6.0	46	48	46	10	16	10
254	198	214	194	419	426	420	29.0	40.0	20.0	44	54	46	3	14	9
253 a	184	199	180	158	185	184	6.0	16.0	4.0	112	96	96	8	17	13
253 b	180	192	186	184	201	208	4.0	12.0	2.0	96	88	88	13	21	10
256 a	134	122	152	154	163	153	1.0	1.0	1.0	56	84	60	3	55	6
256 b	152	142	144	156	178	163	1.0	1.0	0.0	60	90	64	6	64	7
256 c	144	132	134	164	158	165	*0.0	0.0	0.0	64	80	70	7	32	6
256 d	134	129	130	169	172	168	*0.0	0.0	0.0	70	80	76	6	25	3
256 e	130	115	150	172	175	172	*0.0	0.0	0.0	76	84	75	3	30	3
Average	173.3	168.1	173.3	237.5	247.9	250.7	4.9	11.6	5.2	54.7	68.3	55.2	7.1	28.9	7.7

* No outflow. Fluid may have been drawn back into the tube.

† Decreased outflow on stimulation of the sciatic and increased respiration.

‡ Arterial and venous pressures decreased and fluid outflow increased.

limitations of the method employed. Taking an average of the seventeen experiments, the rate of outflow was more than doubled by increasing the respiratory movements. Therefore, the conclusion is warranted that on increasing the respiration by stimulation of the sciatic in a normally breathing dog the outflow of fluid may be increased or decreased, not always decreased as is the statement of Dixon and Halliburton (11) for their experiments where artificial respiration was increased. Their figure 13 (p. 237) as shown in their article does not substantiate their claim that augmented secretion commenced before the respiration was visibly affected, for if the time relations of their recording apparatus are correct, the increased outflow *did* come synchronously with the decrease in amplitude in the respiratory movement, and the maximum was reached at a time when the respiratory movements were approaching the minimum. There was little or no change in the rate of respiration so far as can be judged from their tracing until late during the inhalation and then there was an increase. It has been our experience that by no means does every decrease in the respiratory movements result in an increase in the outflow, nor does every increase in the respiratory movements result in a decrease in the outflow of the fluid. Further, these experiments are inconclusive because they do not measure—at least do not record in their paper—the alterations in the arterial and venous pressures during the experiments involving a decrease in the respiratory movements. Neither do they give the results from more than one experiment, either by this or by the pressure method, an omission sufficient to make their conclusions of little value. It will be noted that in both those cases where there was decreased outflow there was a fall in both the arterial and venous pressures, which may have been the cause of the decreased outflow. On the other hand examination of the table shows that in some of the other experiments where there was a similar fall in both these pressures there was an increase in the outflow. Hence a fall in both venous and arterial pressure is not invariably followed by a decrease in the outflow of fluid, and we believe that the cause of the increased outflow is due in some cases to increase in the arterial or venous pressure or both, accompanied by an increased accumulation of blood in both arterial and venous channels, and in some cases to an increase in the oscillation of the contents of the canal, permitting the outflow of more fluid through the needle, just as more fluid will flow out of a hole in the side of a tank if the fluid in the tank is agitated more strongly. Another explanation is that some of the straits in the intra-

dural canal are always more or less completely occluded by the structures passing through them, thus hindering the free passage of fluid from one portion to the other. Thus if the cranial fossae were full of fluid, increased respiratory movement would, by the rise and fall of the mid-brain during dyspnea facilitate the passage of fluid from the skull cavity to the medullary region and thus increase the outflow from a needle inserted in that region. On the other hand if the cranial fossa were nearly empty, then increased respiratory movements would make easier the passage of fluid from the region of the medulla into the cranial cavity, and thus decrease the outflow. We believe this, together with the alterations in arterial and venous pressures, to be the explanation of the changes observed, these changes being in the nature of either an increase or decrease when the respiration is stimulated by the action of the sciatic. Changes due to alteration of rate and depth of artificial respiration have not been studied, but we do not believe that they will differ from the changes already described. However, they are to be submitted to later study. Thus the decreased flow is due to fall in arterial or venous pressure or both, with less blood in the vessels thus allowing more space for the fluid, and reducing the outflow, or in many cases the fluid may—under the influence of strong respiration—be distributed to distant parts of the canal thus reducing the outflow through the needle. The increase is due to the increases in arterial and venous pressure which displaces more of the fluid, or to the accumulation of fluid in the medullary region by the release of fluid from other parts of the system by movements of the central nervous system.

b. Decreased respiration. Having studied the effects of the increased respiratory movements, we undertook the study of the effect of decreased respiratory movements as produced by stimulation of the superior laryngeal and central vagus. Table 18 shows the effect of stimulation of the superior laryngeal upon the pressure of the fluid. The table shows the results of twelve stimulations performed on three dogs. As can be seen from the tables, the averages of all the pressures rise and then return to the normal immediately after the cessation of the stimulus. The fluid rises relatively more in these animals than for most of the animals shown in this work but in all cases high normal pressures were existent at the beginning of the experiment; thus the canal was full of fluid and the fluid pressure was influenced by arterial as well as venous. If the change in the fluid pressure had been one of secretion then the fluid pressure should have remained high for some

TABLE 18

Effect of the stimulation of the superior laryngeal on the arterial, venous and fluid pressures

TRACING	CIRCULATION AND FLUID									RESPIRATION						DURATION OF STIMULUS
	Arterial			Venous			Fluid			Rate			Amplitude			
	B.	D.	A.	B.	D.	A.	B.	D.	A.	B.	D.	A.	B.	D.	A.	
																seconds
306	108	102	106	238	257	262	222	233	228	24	9	24	3	1	3	41
307 a	118	120	116	341	349	340	334	346	337	52	33	44	3	1	3	12
307 b	116	118	110	329	326	311	328	327	311	44	36	40	3	1	3	22
307 c	108	116	112	306	249	281	308	297	280	40	39	52	3	1	3	38
307 d	108	116	116	279	336	333	277	326	316	50	0	56	3	0	3	22
310 a	168	190	164	130	146	135	189	213	211	32	0	32	15	0	15	15
310 b	144	136	140	116	119	122	205	206	218	44	0	44	12	0	10	26
310 c	142	135	146	127	130	126	228	230	235	52	0	49	10	0	10	20
111 a	144	138	142	126	132	130	236	237	236	26	20	23	10	2	10	22
111 b	142	138	140	131	135	131	231	238	235	23	20	23	10	3	10	22
111 c	140	138	140	132	140	134	236	239	238	23	20	24	10	3	10	47
111 d	140	138	140	133	140	132	238	241	239	24	21	24	10	7	10	45
Average...	131.5	132.0	131.0	199.0	204.9	203.0	252.6	261.0	257.0	36.1	16.5	36.2	7.6	1.5	7.5	

time after the stimulation ceased. Such was not the case; in fact, as can be seen from the table, it fell to almost exactly the same proportional amount as the venous pressure. The venous pressure rose 4.3 mm. and fell 1.9 mm., hence the fall was equal to 44 per cent of the rise. The fluid pressure rose 8.4 mm.—due undoubtedly to changes in the arterial pressure for the fluid pressure was high—and fell 4 mm.

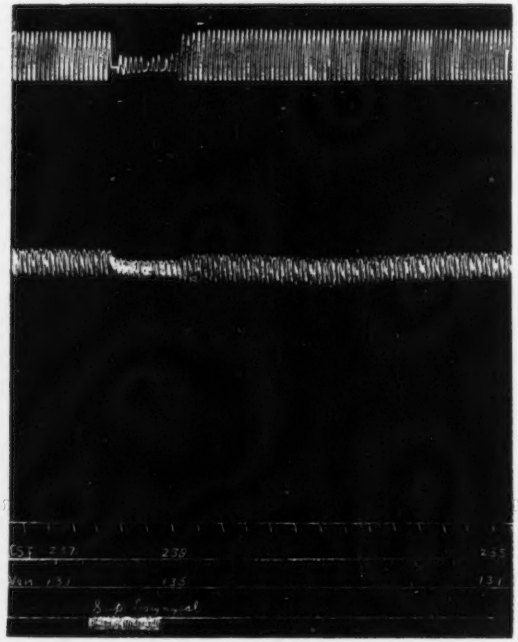

Fig. 18. This figure shows the effect on all the pressures and upon respiration of stimulation of the superior laryngeal nerve.

or 44 per cent of the rise. If the observations had been prolonged until the venous pressure was normal, then the fluid pressure would also have been normal. The period of stimulation varied from 12 to 47 seconds—as long as it is possible to inhibit respiration by such stimulation. (See fig. 18).

Inhibition of respiration by stimulation of the central vagus was carried out. Table 19 shows the results from eight experiments on two

TABLE 19

Effect of the stimulation of the central vagus on the arterial, venous and fluid pressures

TRACING	CIRCULATION AND FLUID									DURATION	RESPIRATION					
	Arterial			Venous			Fluid				Rate			Amplitude		
	B.	D.	A.	B.	D.	A.	B.	D.	A.		B.	D.	A.	B.	D.	A.
										seconds						
312	140	186	140	130	180	136	234	300	238	64	38	46	34	10	7	9
313	140	154	140	138	198	156	236	315	255	158	36	0	17	7	0	9
309 a	190	204	188	149	181	153	158	169	156	38	68	0	76	14	0	14
309 b	192	200	196	142	161	155	144	153	139	45	76	0	68	14	0	14
309 c	190	210	200	144	179	154	139	151	131	45	68	0	68	14	0	14
308 a	138	142	124	317	319	295	294	297	266	22	20	0	20	2	0	2
308 b	124	120	114	289	285	271	261	264	246	77	20	5	28	2	1	2
308 c	112	114	108	259	261	259	239	242	231	45	28	20	24	2	1	2
Average.....	153.2	166.2	151.2	196.0	220.5	197.3	213.1	236.3	207.7		44.2	8.8	41.8	8.1	1.1	8.2

animals. The inhibition was maintained from 45 to 158 seconds, ample time—according to Dixon and Halliburton—for asphyxiation or CO_2 to have its effect upon the mechanism forming the fluid. The changes, as might be expected, are much greater than those secured from stimulation of the superior laryngeal, because of the greater number or the greater effectiveness of the afferent fibers in the vagus trunk. The arterial, venous and fluid pressures all rose with the beginning and fell with the termination of the stimulation. The changes in all the fluids are rapid, synchronous, in the same direction, and to some degree proportional. Therefore, the changes are all due directly or indirectly to the effect of the pressor fibers, and the changes are purely mechanical in origin, coming from changes in the blood pressure. Much work remains to be done on this phase of the subject, but the data we have given are ample to prove that the conclusions of Dixon and Halliburton regarding the influence of CO_2 in stimulating the structures forming the fluid are too sweeping, being based upon the results from experiments too few in number and not sufficiently controlled to warrant the broad conclusions they have drawn. We have experiments exactly like those shown by these authors. The conclusions drawn from their graphs would be correct if the graphs were typical of a larger number of experiments, but they are not, as can be seen by reference to our tables given above. Whether the outflow method they employed or the manometer method is correct has already been discussed (see fig. 19).

Asphyxia. The effectiveness of asphyxia as a stimulant of the mechanism forming the cerebrospinal fluid has recently been emphasized. Dixon and Halliburton using the outflow method state: "asphyxia always leads to considerable increase in outflow." This they believe due to the CO_2 of the alveolar air, and point out that in this respect the choroid does not behave like a secretory gland, for most glands secrete more rapidly when the blood is well aerated. They state that drugs such as nitrites and nitrobenzenes which rapidly produce methemoglobin also cause the secretion to increase. In their later article dealing with fluid pressure they claim that torcular pressure rises slowly at first during asphyxia, and then more rapidly, and continues to rise when the arterial pressure falls and the heart fails. The cerebrospinal fluid pressure rises slowly at first, but more rapidly later. The fluid pressure commences to fall before the arterial blood pressure has reached its maximum (fig. 20).

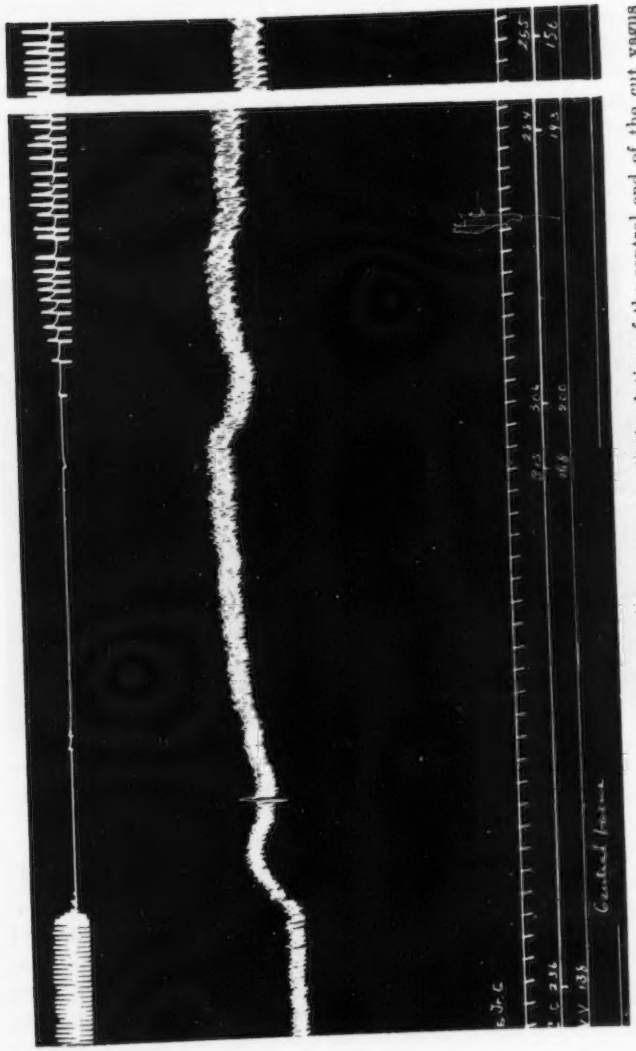

Fig. 19. This figure shows the effect on all the pressures of stimulation of the central end of the cut vagus nerve.

We show in table 20 the beginning, maximum and end pressures in eight animals well anesthetized and killed by asphyxia produced by opening one or both pleural cavities by large incisions parallel with and between the ribs. We preferred this method to deep anesthetization, because with the interruption of artificial respiration the latter method will produce too marked a depression of the centers of the medulla. Using this method of study we found that torcular venous pressure rose with the asphyxial rise in arterial pressure, and this rise of venous pressure persisted after arterial pressure had fallen to zero.

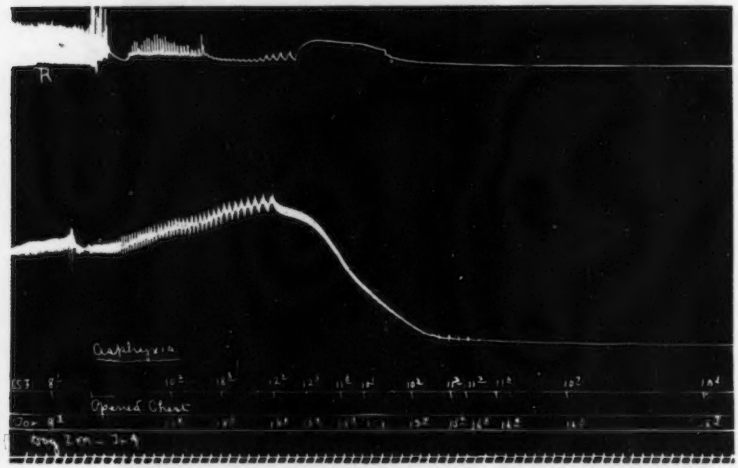

Fig. 20. This figure shows the effect of opening the chest (asphyxia) upon the respiration, arterial, venous and fluid pressures. The animal was under moderate surgical anesthesia.

It was our experience that fluid pressure ran a course parallel with the venous pressure. Venous pressure rose on the average 67.9 mm. and fell 44.5 mm. Fluid pressure rose on the average 71.0 mm. and fell 53.5 mm. The venous pressure fall was 65 per cent of the venous rise, and fluid fall was 75 per cent of the fluid rise. In other words, these two pressures run a remarkably parallel course, both remaining above the normal. Where the outflow method is used this might in many cases result in increased outflow of fluid. In figure 20 we show a typical result. Note that venous and fluid pressures run a remarkably parallel

course. There are two maxima in the curves, and while not absolutely synchronous they fall closely enough together for the phenomenon to be significant. The first maximum in fluid pressure undoubtedly came early because of the marked rise in arterial pressure, for arterial pressure does influence fluid pressures in some animals, as has already been shown.

In accordance with the findings shown in table 20 and figure 20, we believe that all the changes observed in fluid pressure during asphyxia are logically explained by the changes in arterial and venous pressures. Thus it is unnecessary to assume new formation under the influence of carbon dioxide.

TABLE 20

Asphyxia. This table records the variations in arterial, venous and fluid pressures between the opening of the chest and the death of the animal. Note that the pressures all rose and then fell, but the fall in arterial was much greater than the fall in venous and fluid pressures

ARTERIAL			TORCULAR VENOUS			CEREBROSPINAL FLUID		
B	D	A	B	D	A	B	D	A
120	144	30	92	156	157	81	188	106
80	126	42	65	170	84	24	160	38
120	152	124	102	136	134	104	142	141
64	132	128	68	145	110	58	133	92
94	118	22	205	240	165	87	140	82
80	84	44	79	119	56	87	130	56
112	180	16	38	232	131	25	142	102
80	86	8	116	110	115	113	112	102
Average 93.7	127.7	59.1	95.6	163.5	119.0	72.3	143.3	89.8

IV. THE NORMAL RATE OF THE FORMATION OF THE CEREBROSPINAL FLUID AND ITS ABSORPTION

Formation

Logically, the first question to settle in this problem is the normal rate of the formation of the cerebrospinal fluid. Various estimates have been given. Dixon and Halliburton (11) record the rate in the dog as averaging about 6 cc. per hour in an experiment lasting almost three hours; in the goat as varying between 13.5 cc. during the first hour to nothing after the fifth hour. The decrease was gradual. We assume that these figures do not include the fluid which escaped when

the membranes were first punctured. Frazier and Peet (7) obtained from a dog of 10 kilo weight 1.66 cc. in 7 minutes and 10 seconds, or 0.231 cc. per minute; from a dog of 8 kilo weight they obtained 3.57 cc. in 18 minutes, or 0.192 cc. per minute. They had drained the canal 10 minutes before the observations were begun. In these experiments, also, the rate decreased during the experiment.

Recalling the errors of method pointed out above, it is easy to see that this so-called "normal rate" of flow recorded by these authors may have no relation whatever to the normal rate of formation of fluid. This flow may represent the slow *leakage* past obstructions in the canal of fluid not removed by the preliminary drainage, a leakage made possible by the rhythmical movements of the cord and medulla, produced by the respiratory and cardiac impulses. Since these movements are uniform the rate of leakage is uniform but gradually decreasing as the reserve is exhausted, and finally ceasing entirely. This interpretation of the flow easily explains the observation of Dixon and Halliburton that the flow in the goat ceased entirely after the fifth hour although the blood pressure was still 80 mm. of mercury, and they had "frequently noted abundant secretion at a much lower pressure." On the other hand, the flow may represent *transudation*, not the normal formation, transudation from the meninges or other vascular structures of the dural canal as a result of the decreased intracranial pressure produced by the more or less complete drainage fluid. Frazier and Peet point out the importance of this factor in commenting on the clinical observations in compound fracture of the skull, but failed to apply their criticism in the selection of a method for their own experiments. Of course if the criticism is valid in the clinical cases it is valid in the laboratory experiment. Of the two factors, it seems probable the first—leakage of preformed fluid—is more important in experiments of short duration like those cited above; while the second—transudation from reduced intracranial pressure—is more important in experiments of long duration, into which class the clinical cases fall.

In the course of our work we had ample opportunity to study the "rate of formation of the fluid" according to the methods of the authors mentioned. Several experiments were done to determine this point specifically. However, after considering the situation fully we decided that the data did not bear upon the point at all. We could and did measure the rate at which the fluid would drop from a needle inserted into the canal, or would run out into a glass tube connected with the

needle, but that in our opinion does not measure the rate of formation of the fluid. Neither the tube nor the manometer method, nor any other method we have seen described is suited to make this apparently simple determination. All that has been measured is the rate at which fluid can be moved about in the canal, or the rate at which it can be formed under reduced pressure within the skull. If an animal is observed over a long period of time, only slight variations of the level of fluid occur, so long as the level of venous pressure remains unchanged and the respiration is constant. If the anesthetic is reduced, so the venous blood pressure rises and the respiration increases, then the fluid rises in the tube. When the anesthetic is increased, and venous blood pressure and respiration decrease, the fluid falls in the tube. In experiments lasting from three to five and one-half hours the change of fluid levels are negligible so long as the venous blood pressures remain the same. The explanation of the constancy of the fluid levels is easy. Normal conditions within the skull are retained and hence formation and removal of fluid take place by the normal mechanism, and at the normal rate, and therefore balance exactly. Only when vascular changes take place rapidly does the level of fluid vary to any great degree. These changes of course are measured readily, and their influence upon the level of the pressure of the cerebrospinal fluid can be estimated.

When the manometer method is used the same results are obtained; there are no changes which can not be explained by the change in blood pressure.

Without being able to give direct and convincing evidence on this point on account of the lack of a suitable method, we believe that the normal rate of formation of the fluid is a relatively slow process, much slower than the statements of the clinicians and the experiments cited above from other workers would lead one to believe. We do not wish—as the above statement seems to do—to put this problem out of the realm of experiment, but it seems to occupy that place because of the lack of a suitable method.

Attempts to get at this problem indirectly have led to questionable and we believe erroneous conclusions. Frazier and Peet, working with phenolsulphonephthalein found that if the drug is injected into the ventricles "under normal conditions about 50 to 60 per cent is excreted into the bladder within two hours." They then conclude: "If we can assume that the cerebrospinal fluid is absorbed proportionally as rapidly as the amount of phthalein injected, *and there is no reason*

for believing otherwise, we are led to the conclusion that at least 50 to 60 per cent of the cerebrospinal fluid is absorbed every two hours." We cannot agree with this conclusion. The absence of proof that an assertion is untrue does not prove that the assertion is true. In this instance it cannot be assumed, it must be proved, that all of the constituents of the cerebrospinal fluid are absorbed in the same proportion to the whole as the drug; otherwise the possibility of the selective absorption of a foreign material is not eliminated. It would be just as sound reasoning to assume that since from 50 to 60 per cent of the phenolsulphonephthalein has been excreted from the blood by the kidneys in two hours that 50 to 60 per cent of the water and other constituents of the blood had been eliminated in that time. Assuming the weight of the blood to be one-tenth of that of the body for animals, and the blood to be two-thirds plasma, than in a man of 60 kilos weight there should occur in 2 hours the excretion of 2 to 2.4 liters of urine, or 24 to 28.8 liters in 24 hours. This of course is preposterous and proves that the drug must be selectively excreted from the kidney and is not excreted in proportion to all the other constituents of the blood. This same activity must be proved to be absent from the cerebrospinal mechanism before the conclusions of Frazier and Peet become at all convincing.

Dandy and Blackfan (6) made observations on the same field at about the same time. Their results are in accord with those of Frazier and Peet but from their findings they drew no conclusions regarding the rate of removal and hence of formation of the cerebrospinal fluid.

We do not claim to have proved a specific absorption of pilocarpine from the dural canal but using the submaxillary gland as an index of the presence of the drug in the blood, we did establish the fact that absorption of this drug from the canal is approximately the same in rate as from other internal cavities of the body. (See tables 21 and 22).

From table 21 it becomes evident that absorption from the dural canal of pilocarpine, or rather its transfer into the blood stream, is accomplished after about the same latent period as the transfer from the bowel, pleural or peritoneal surfaces. Since the transfer from these surfaces is in all probability by specific absorption of the drug *per se*, it follows that so far as the time element is concerned there is nothing against the transfer of the drug from the canal to the blood by the same process. As was stated above we are fully aware of the fact that this does not *prove* that drugs are specifically absorbed from the canal. In this connection it was considered important also to study

TABLE 21

Rate of absorption of pilocarpine. Wharton's duct was used unless otherwise indicated

DOG	MODE OF APPLICATION	LEFT DUCT	RIGHT DUCT	REMARKS
		minutes	*minutes*	
1a	Intradurally	4.83		
2a	Intradurally	4.09		
3a	Intradurally	3.68	3.78	Right chorda cut
1	Intramuscularly	0.78	0.87	
2	Intramuscularly	1.00	1.04	
3	Intraperitoneally	3.00	3.20	
5	Intraperitoneally	2.7	2.9	
6	Intraenterally	2.05	2.9	
9	Intraenterally	11.0	12.0	
7	Intrapleurally	5.2	3.6	
8	Intrapleurally	4.2	3.8	
10	Subcutaneously	2.15	2.13	
11	Subcutaneously	4.51	3.11	Left duct twisted
12	Subcutaneously	4.45		
13	Subcutaneously	3.4	3.2	
15	Intraocularly		4.25	
16	Intraocularly		3.08	

TABLE 22

Latent period of the absorption of atropine from the dural canal as judged by the effect of the drug on the submaxillary gland and the heart. The circulation and the gland had previously been influenced by the injection of pilocarpine

TRACING	GLAND	HEART
	minutes	*minutes*
1	1.0	2.18
2	6.6	*
3	2.58	*
4	1.55	0.50
5	1.86	*
6	0.75	1.25
7	4.35	*
8	1.63	*
9	4.33	*
10	0.43	0.41
11	0.33	0.33
Averages.....	2.31	0.93

* Beginning of action not clearly marked.

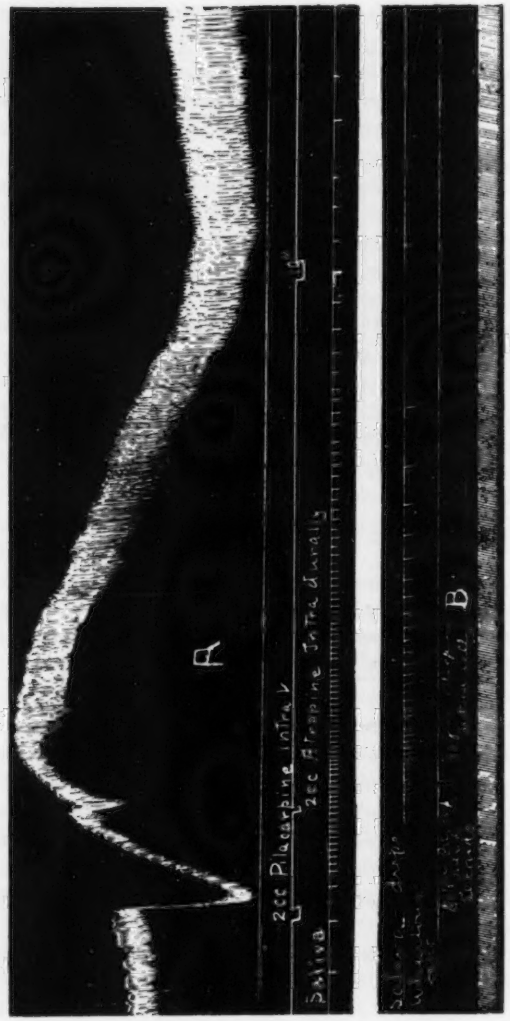

Fig. 21. This figure shows the rate of absorption of pilocarpine and atropine from the dural canal. Note that the latent period is about twice as long when the drug is given intradurally as when given intravenously. The rate of speed is about the same in both *A* and *B*.

latent periods of absorption of atropine from the dural canal. As may be seen from the table, there is a wide variation in the duration of this period independent of any known cause, for the injections were always made in exactly the same way, and in equal amounts in all the animals. A cannula was placed in Wharton's duct and the chorda lingual was stimulated electrically until saliva dropped from the end of the tube. The animal was then injected subcutaneously with pilocarpine, and the cardio-inhibitor and salivary mechanism thrown into activity. Then atropine was injected intradurally and the release of the heart from inhibition and the cessation of salivary flow observed. As is well known it is not always possible to judge the exact moment of release of the heart from the inhibition mechanism; for that reason but few observations were made on that point. The results of eleven experiments are shown in table 22 and in figure 21.

Since obvious error in the direct experiments can be pointed out, since the conclusions regarding the rate of formation based upon the rate of excretion of phenolsulphonephthalein can be shown to be unwarranted, it becomes evident that the normal rate of formation of the fluid has not been determined.

Absorption of the fluid and its contents

Literature: It has long been known that substances like dyes injected into the subarachnoid space, find their way into the blood. From experimental evidence it seems that the absorption is by way of the blood stream rather than by the lymphatics. Further, there is evidence for believing that no direct communication between the subarachnoid space and the blood vessels exists, hence the transfer from this space to the blood is by filtration, by diffusion or by direct and specific absorption. Since the hydrostatic pressure is usually—some say always—higher in the blood vessels than in the fluid, it is evident that filtration cannot be the mechanism of transfer, hence diffusion and specific absorption are left as the only alternatives. Dixon and Halliburton (29) in a recent article claim to have established the fact that substances which disappear from the fluid do so by a process of diffusion. They assume that a molecule of adrenalin is smaller than a molecule of secretin, and that a molecule of secretin is smaller than a molecule of peptone. Then they claim to have shown that the rate of transfer of these substances to the blood is slower or faster in proportion to the size of the molecule of the substance they are studying. That their work does

not prove the point will become evident. The point at which the transfer from the canal to the blood takes place is still a matter of controversy.

The rate at which this transfer takes place has been studied for years. Much of this work is of no value from the standpoint of a study of the normal, because of the abnormal pressures used in producing the results. The present communication deals with the absorption of drugs at or near normal pressure conditions.

Lewandowsky (30) studied the absorption of strychnine and other substances from the dural canal, and concluded that these drugs entered the nervous system by direct absorption from the cerebrospinal fluid, because he could produce typical results with smaller doses by this method than by the ordinary route—by subcutaneous injection.

A further study (31) showed that it was possible, by intradural injection of strychnine, to produce local areas of hyperexcitability in the cord without influencing remote areas. This also points to direct absorption of the drug by the nervous tissue from the fluid instead of from the blood, for in the latter case all parts of the nervous system would be simultaneously and proportionately affected.

Meltzer and Auer (32) studied the effect of the intradural injection of adrenalin in six monkeys, used repeatedly, with several days intervening between experiments. Twenty-one injections were made in all. They concluded that intradural injections do *not* produce the typical effects of an intravenous injection. Thirteen of these injections gave a rise in blood pressure, slow in making its appearance and of long duration. In six cases a fall preceded the rise, and in one case the fall was the only effect. In seven cases there was a rise similar to that seen on intravenous injection. They suggest that this rise is due to some of the solution entering a vein at the time of the injection. Recently (33) these same writers have restated these same facts with additional proof.

Dixon and Halliburton in their last paper on the fluid state: "after an injection (of adrenalin) into the subcerebellar cisterna, a short latent period ensues of from ten to thirty seconds, then cardiac acceleration becomes obvious (the vagi being cut) and the blood pressure rises." Regarding nicotine they say: "Nicotine in doses of from one to two milligrams acted like adrenalin on the vascular system, and was readily absorbed from the cerebrospinal fluid into the blood." In support of this statement they give a tracing of the action of each drug which shows the blood pressure curves of intravenous and intradural injection almost superimposed. From these findings supplemented by observations

upon substances with a supposedly larger molecule like secretin and peptone, and upon crystalline substances and dyes, they draw the following conclusions: "If these substances (introduced into the fluid) are readily diffusible the speed with which they appear in the blood is very remarkable. . . . An injection of substances like adrenalin, nicotine and atropine produces characteristic physiological effects almost as rapidly as if injected in the venous circulation. Substances which are not diffusible such as proteins . . . . . do not produce their characteristic effects, when introduced into the cerebrospinal fluid. Whereas substances of intermediate molecular size, such as secretin, diffuse slowly, and cause their action at an intermediate rate." Numerous other conclusions were drawn. The conclusions regarding the action of adrenalin and nicotine as drawn by Dixon and Halliburton are warranted from the tracings they publish. But the writer is convinced that the facts regarding the action of these two drugs are not as stated by the authors quoted.

Experiments: In experiments carried out on twenty-one animals into which forty separate series of injections were made, twenty-seven of which were with adrenalin, thirteen with nicotine, in only two instances did the arterial pressure rise in the manner described by Dixon and Halliburton as the usual result of the injection. In both cases this rise followed the injection of adrenalin, and in both cases the cerebrospinal fluid was bloody when fluid was withdrawn as a preliminary step to the injection of the drug. In one of these cases a later injection of adrenalin was followed by a fall instead of the rise described as characteristic by the authors cited. We are forced to the conclusion that some error was made by the authors probably in the injection of the drug which resulted as suggested by Meltzer in his own work, in the entrance of a part of the solution into the blood stream, probably in this case by way of some of the intracranial veins, with the production of a characteristic rise in the blood pressure. We noted the results given in two cases and were able to produce results in two others like those reported by them as the normal, but in the four cases in which this rise was noted the fluid was bloody in two, and a communication existed between the subarachnoid space and the torcula in two. It was shown by experiment that animals with the vagi cut behave in a manner similar to those which have been atropinized.

The methods employed were exactly similar to those used by Dixon and Halliburton, with the exception that we atropinized the animals instead of cutting the vagi. In addition instead of using a fresh solu-

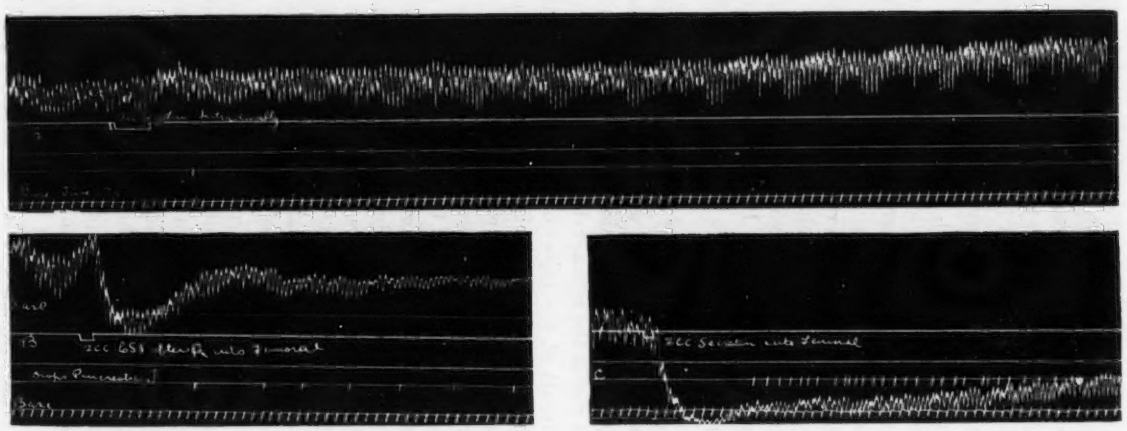

Fig. 22. This figure shows the difference in the rate of absorption of secretin intradurally and intravenously. Note that *A* shows the effect of the intradural injection of 3 cc. of neutralized secretin solution with no response from the pancreas although 12 minutes elapsed before the end of this tracing. Note in *B* the response from the intravenous injection of 2 cc. of the spinal fluid from this animal, showing clearly that the secretin was in the canal. Note in *C* the response from the intravenous injection of 2 cc. of the original secretin solution.

tion of the drug for the intravenous injection, we frequently withdrew some of the cerebrospinal fluid after the intradural injection of adrenalin and injected that intravenously, because by this method it was rendered certain that the drug was in the canal. The number of experiments performed by these men must have been small, otherwise they would have noted and corrected their error. We did not follow the long-continued action of intradural injections of adrenalin in enough animals to prove or disprove Auer and Meltzer's findings. We believe them correct. In one case we followed for 6½ hours the blood pressure

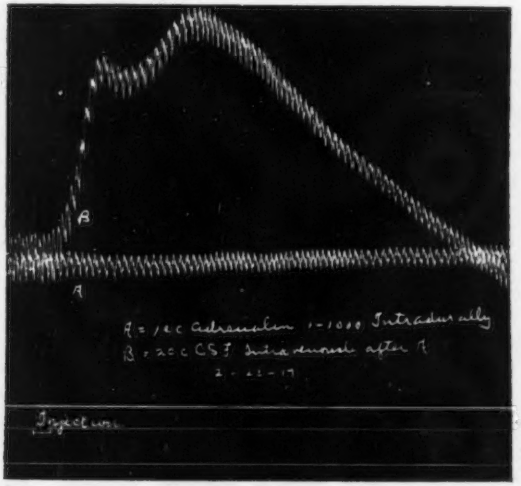

Fig. 23. This figure shows the effect of: *A* the injection of 1 cc. of adrenalin chloride intradurally; *B* the effect of the injection of 2 cc. of cerebrospinal fluid from the same animal intravenously. The fluid was withdrawn after it had been in the canal 8 minutes. *B* was made 10 minutes after *A*.

was practically constant throughout. The result of the other is shown in figure 24.

In proof of our conclusions that adrenalin and nicotone do not produce a rise in the blood pressure when injected intradurally we submit the following tables and graphs. The tables include the observations made on *all* the animals used in this particular part of the work. The graphs are the results of a few of the experiments. The effect of the intradural injection of adrenalin is shown in table 24 and figures 23 and 24.

As will be noted in the data, in only one case was the intradural injection of adrenalin followed by a marked rise in the blood pressure and in that case the latent period was longer than on intravenous injection and the fluid was bloody. A similar rise occurred in another case which was observed in some other work.

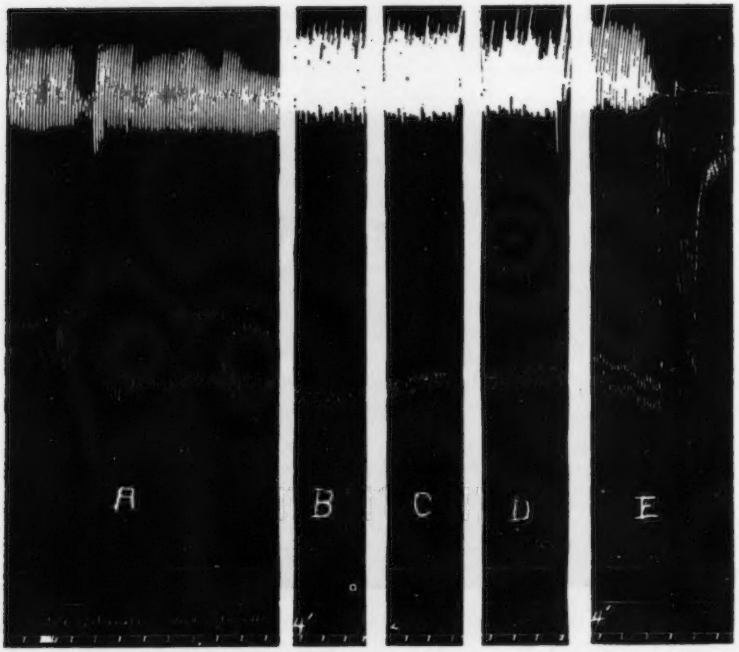

Fig. 24. This figure shows a long time (about 20 minutes) experiment after the intradural injection of 2 cc. of adrenalin chloride (1–1000). Four minutes elapsed between *A* and *B*, between *B* and *C*; and *C* and *D*. No rise in blood pressure occurred. After *D* was completed 8 cc. of the fluid of the animal were withdrawn at the occiput and injected intravenously, as shown in *E*, with a typical adrenalin effect on the blood pressure.

The effect of intradural injection of nicotine is shown in table 24 and figure 25.

In the case of the thirteen injections of nicotine in not a single case was there the characteristic rise in the blood pressure.

As will be noted in every case where the experiment is free from criticism, adrenalin and nicotine injected intradurally produced no characteristic rise in the blood pressure; and in every case the injection of the fresh drug or of the fluid withdrawn from the canal and injected intravenously produced characteristic results upon the blood pressure.

TABLE 23

This table shows the effect on the circulation of intradural injections of adrenalin chloride (P. D. & Co.), also the effect of intravenous injection of adrenalin chloride or of the cerebrospinal fluid of the animal after intradural injection. Tracings 1 and 2, dog 21, were from a dog without atropine with the vagi cut

DOG	TRACING	INTRADURAL INJECTION			LATENT PERIOD OF INTRAVENOUS INJECTION WITH TYPICAL EFFECT	
		Effect	Observation period		Adrenalin	C. S. Fluid
			minutes	*seconds*	*seconds*	*seconds*
1	1	None	4	36	8.3	
1	2	None	4	36	4.6	
2	1	Slight rise	4	36	9.4	
2	2	None	4	36	11.1	12.2
3	1	Slight fall	9	37	10.0	
3	2	Slight fall	10	0	13.3	
3	3	Slight rise	10	0	10.0	
4	1	None	7	30		10.0
5	1	None	7	0		12.0
6	1	Slight fall	8	0		12.0
7	1	Slight fall	14	0	7.5	
7	2	Slight fall	14	0	10.3	
8	1	Slight rise	4	0	13.0	
9	1	Slight fall	2	15		11.6
10	1	Great rise*	5	30		8.3
11	1	None	3	0	26.0	10.0
12	1	None	3	0		11.0
13	1	Slight rise	2	40		22.0
14	1	None	2	30		5.0
15	1	None	2	0		8.4
16	1	None	2	3		13.3
17	1	Slight fall	4	0		10.0
18	1	Slight rise	2	0		20.0
19	1	Slight fall	2	40		10.0
20	1	Slight fall	4	0		15.0
21	1	Slight rise	7	0		3.0
21	2	None	7	0		5.0

* The fluid from this dog was bloody.

Therefore the absence of effect after subdural injection is due to the lack of central action of the drugs and to a lack of absorption from the space; it is not due to a failure to inject the drug into the canal, to inactivity of the drug or to a failure of response on the part of the animal. The effect of the intradural injection has already been discussed.

After proving conclusively that adrenalin intradurally had no effect upon the blood pressure comparable to the effect intravenously, the work of determining the length of the stay of the drug in the canal was

TABLE 24

This table shows the effect on the circulation of intradural injections of 0.025 per cent nicotine, also the effect of the intravenous injection of the same drug, or the cerebrospinal fluid of the animal drawn after the drug had been permitted to act for some time

DOG	TRACING	INTRADURAL INJECTION			LATENT PERIOD OF INTRAVENOUS INJECTION WITH TYPICAL RESULTS	
		Effect	Observation period		Nicotine	C. S. Fluid
			minutes	*seconds*	*seconds*	*seconds*
3	3	None	10	0	13.3	14.4
4	2	None	7	30		17.0
5	2	Fall*	7	0		12.0
6	2	Slight fall	2	40		6.3
9	2	Slight fall	1	24		17.0
10	2	Slight rise	4	10		10.0
11	2	Slight fall	2	40		15.0
12	2	Slight fall	2	30		12.0
13	2	Slight fall	1	40		9.2
14	2	Slight fall	2	0		13.3
15	2	Slight fall	1	40		10.0
16	2	Slight fall	2	0		13.3
20	2	Fall*	4	0		10.0

* The fall in blood pressure in these cases amounted to about 30 mm. of mercury. In all the other cases the fall was insignificant and transient.

begun. The work was done in two steps. In this series four dogs were used. From each of four dogs, two under ether and two under morphine, 3 cc. of fluid were drawn, and the same amount of adrenalin chloride (P. D. & Co.) introduced. At 30 minute intervals for two hours 1 cc. of fluid was withdrawn and tested by intravenous injection into a dog. In each case the pressure of adrenalin was demonstrated by a typical rise in the blood pressure on the intravenous injection of the fluid. These experiments prove that adrenalin remains in the canal for at least two hours.

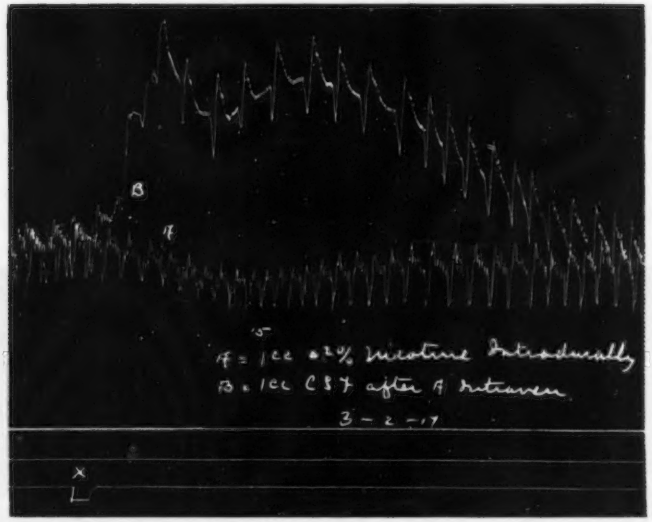

Fig. 25. This figure shows the differences in the reaction of the blood pressure to nicotine injected intradurally, and to the cerebrospinal fluid of the same animal injected after withdrawal from the canal. At *A*, 1 cc. of 0.2 per cent nicotine was given intradurally. At *B* (15 minutes later), 1 cc. of the cerebrospinal fluid from this animal was given intravenously. Injections were made at *X*.

In the second step of the experiment, three dogs were used. The details of one experiment were enough to show the results of the group:

Dog A 31, weight 15 kilo

8: 20 Animal anesthetized.
8: 24. Needle inserted into the *cisterna magna;* 5 cc. of fluid were withdrawn, and 5 cc. adrenalin chloride (P. D. & Co.) injected. No spasms. Animal quiet during recovery.
8: 59. Animal fully recovered. Drowsy.
11: 20. Animal re-anesthetized. Tracheal cannula inserted.
11: 24. 1 cc. of cerebrospinal fluid drawn. Fluid clear.
12: 24. 1 cc. of cerebrospinal fluid drawn. Fluid clear.
1: 24. 1 cc. of fluid drawn. Fluid slightly red in color. No blood.
2: 24. 1 cc. of fluid drawn. Fluid slightly red in color. No blood.
3: 00. Animal killed with ether.

Dog A 32, weight 5 kilo

2: 30. Animal anesthetized.
2: 45. Tracheal cannula and blood pressure cannulae inserted.
2: 45 to 4: 00 p.m. Fluids from dog A 31 injected one after the other.

This experiment shows conclusively that adrenalin is present in the fluid for five hours. The fluid drawn at the sixth hour gives a doubtful result, for the rise is very small, practically none. This finding has been confirmed exactly by experiment in two other animals. Therefore,

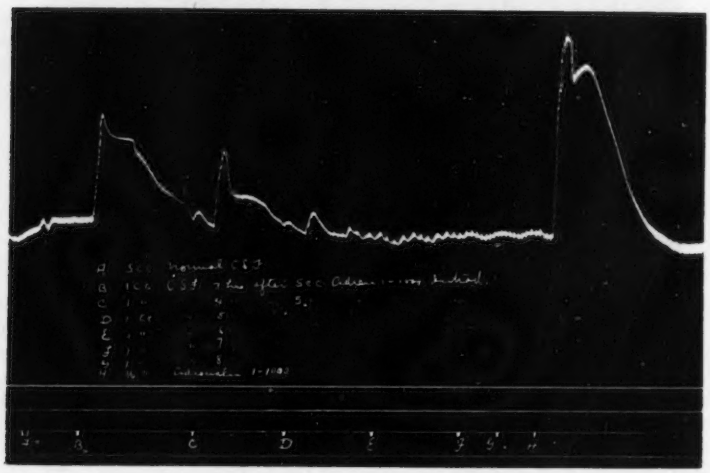

Fig. 26. This figure shows the effect of the repeated injections of 1 cc. of cerebrospinal fluid from dog A into dog B. The fluid was drawn at varying intervals 3 to 8 hours after 5 cc. of the cerebrospinal fluid of dog A had been replaced by adrenalin chloride. The graph shows a positive reaction in dog B at least 5 hours after the drug had been injected, and hence adrenalin must remain in the canal for at least that period.

adrenalin remains in the dural canal for at least five hours. The fact that adrenalin can be detected in the canal for five hours weakens the proof of Dixon and Halliburton that it passes out of the canal into the blood stream with the extreme rapidity they described in their last paper, for otherwise we might expect it all to be gone long before five hours have elapsed. (See fig. 26).

A further study was begun in order to determine the fate of adrenalin after injection of the drug into the dural canal. The possibility

that a part of the adrenalin was destroyed in the canal and thus prevented from ever reaching the blood stream was also considered. To determine whether any of the adrenalin was lost by this method mixtures of adrenalin chloride and cerebrospinal fluid were made. It was estimated that in a large dog there might well be 50 cc. of the fluid in the canal. So if 5 cc. were drawn and replaced by adrenalin chloride, the ratio of 5 in 50 or 1 to 10 of adrenalin chloride and cerebrospinal fluid would be obtained. With that conclusion in mind we made the following mixtures:

(1) 0.1 cc. adrenalin chloride 0.1 cc. of cerebrospinal fluid 1 to 2.
(2) 0.1 cc. adrenalin chloride 0.9 cc. of cerebrospinal fluid 1 to 10.
(3) 0.1 cc. adrenalin chloride 1.9 cc. of cerebrospinal fluid 1 to 20.
(4) 0.1 cc. adrenalin chloride 2.9 cc. of cerebrospinal fluid 1 to 30.

These tubes were incubated for 7 hours and 15 minutes at 37.5°C. At the end of that time the contents of the tubes were made up to 2 cc. in each case, and injected intravenously into a pithed cat, one after the other. The results are shown in figure 27.

As is seen in the figure, the mixture in tubes (1) was almost inactive, (2) showed considerable activity, (3) showed still more activity, and (4) was most active of all, because it can be seen that the curve is flatter on top. However, all were less active than 0.1 cc. of adrenalin without incubation, and less active than the same amount of the drug incubated in 1.9 cc. of a NaCl solution. Dilution of a mixture of 0.1 cc. of adrenalin and 1.9 cc. of the fluid by the addition of 1 cc. of salt solution before being incubated did not affect the destruction of adrenalin. We have here a peculiar phenomenon in which it is evident that small amounts of the fluid produce the destruction of adrenalin, while larger amounts produce less destruction of the drug. A parallel series with blood substituted for the fluid showed that small amounts of fluid produced greater destruction of adrenalin than an equal amount of blood. Here is a problem requiring more work to determine the factors involved. If the 1 to 10 ratio is correct, it is unnecessary that more than one-half of the adrenalin be absorbed, to account for the loss of adrenalin from the canal, for in that ratio at the temperature of the body, most of the adrenalin in the mixture of fluid and adrenalin is destroyed *in vitro*. This is shown by the fact that a mixture of fluid 0.9 cc. and adrenalin 0.1 cc. after incubation for 7¼ hours produces only one-fourth the rise produced by such a mixture before incubation, and about one-third the rise produced by the same amount of adrenalin incubated with

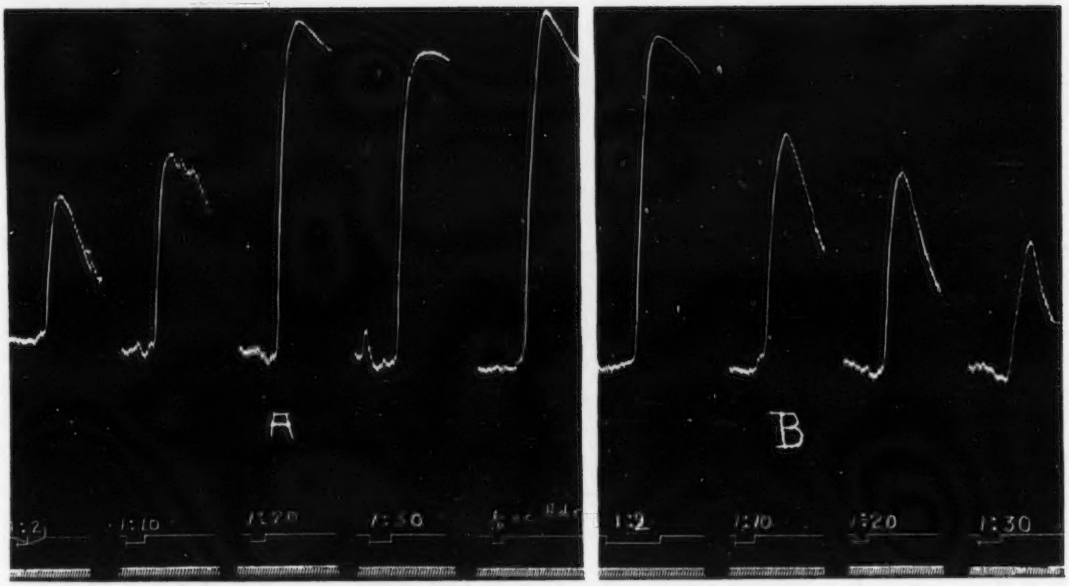

Fig. 27. This figure shows the effect on the blood pressure of a pithed cat of the injection of $\frac{1}{10}$ cc. of adrenalin which has been incubated for 7 hours with varying amounts $\frac{1}{10}$ cc. to $1\frac{9}{10}$ cc. of cerebrospinal fluid of a dog. Note in *A* that the greater the dilution with fluid the greater was the amount of adrenalin remaining after this period of incubation. Note in *B* that with salt solution, the opposite is the result, the greater the dilution with salt solution the less was the amount of adrenalin remaining after this period of incubation. The change was probably one of oxidation for the solutions were appropriately discolored.

blood. It is evident that in an experiment, uncomplicated by intravenous injection, simultaneous with the intradural injection, the absorption from the canal is slow, so not more than one-half of that injected need be absorbed to account for the loss from the canal, the rest having been destroyed by the fluid. Meltzer (34) noted the destruc-

Fig. 28. This figure shows the effect of heating to 65° or 70°C. the cerebrospinal fluid, before mixing it with the adrenalin, upon the reaction shown in figure 27. The "oxidizing power" remains, but the protective power is lost so that the dilution of adrenalin with fluid in any amount results in the destruction of adrenalin in all dilutions.

tive power of fluid for adrenalin but failed to note the protective power of the larger doses.

Conclusions: Adrenalin and nicotine are not adsorbed from the dural canal rapidly enough to produce characteristic vascular responses. Hence the findings of Dixon and Halliburton regarding the rate of ab-

sorption are clearly in error. This error is due probably to faulty technique in the injection of the adrenalin intradurally and to the observation of too small a number of animals.

Adrenalin injected into the subdural space can be detected for at least six hours by its effect on the vascular system of the dog. It can be shown by a test experiment that relatively large amounts are destroyed by the cerebrospinal fluid at 37.5°C. in that time, hence if allowance is made for loss by destruction, relatively little of the fluid need be absorbed to account for the disappearance of the drug from the canal.

Small amounts of the cerebrospinal fluid are more active in destroying adrenalin chloride (P. D. & Co.) than large amounts.

Since substances with supposedly small molecules like adrenalin and nicotine do not pass readily from the canal, it was hardly considered necessary to study the passage of less diffusible substances like secretin and peptone to warrant us in the statement that the conclusion of Dixon and Halliburton that the transfer must be by diffusion is not warranted by the facts, for none of the substances pass out rapidly. However, a series of experiments on the intradural injection of secretin was carried out. In no case was there any secretion of pancreatic juice after intradural injection, although the preparation used was active after intravenous injection. The fluid drawn after allowing 12 minutes time for absorption was also active. (See fig. 22.)

Since the conclusions are based on faulty observations there is, from Dixon and Halliburton's work, no evidence regarding the location or mechanism of absorption.

V. THE EFFECT OF DRUGS ON ARTERIAL, VENOUS AND FLUID PRESSURES

Drugs stimulating the secretion of glandular organs

a. Pilocarpine. Literature: Of all the drugs having the power of stimulating the secretory mechanism of animals to activity, pilocarpine possesses this action to the highest degree. To a slighter degree this power is shown also by eserine, nicotine and arecolin. Thus if a secretory response on the part of the mechanism forming the fluid is to be expected in any case, it is to be expected of pilocarpine.

Cappelleti (2) studied the outflow of fluid by the fistula method and concluded that pilocarpine stimulated the outflow of fluid.

Dixon and Halliburton (11) in their first paper were very doubtful in regard to the stimulating action of pilocarpine on the mechanism forming the fluid, and listed this drug among those where the true result might be masked by respiratory or vascular changes.

These same authors (12) in their second article concluded that pilocarpine had a direct stimulating effect upon the mechanism forming the fluid, for they believe to have shown the fluid pressure to be independent of the cerebral venous pressure.

TABLE 25

This table shows the effect of the injection of pilocarpine upon the various pressures under consideration. Note that the behavior of the pressures in the last three experiments is not materially different from the others, although the jugulars had been tied

	ARTERIAL				VENOUS				CEREBROSPINAL FLUID			
	B	D		A	B	D		A	B	D		A
		1	2			1	2			1	2	
1	156	130	200	152	82	95	113	85	128	129	159	117
2	100	74	140	108	52	52	84	50	51	51	81	50
3	96	8	162	118	106	162	192	102	105	146	180	102
4	170	38	196	158	150	179	247	178	136	152	187	128
5	126	78	148	100	121	126	156	101	126	116	159	109
6	160	20	124	110	129	125	155	147	164	160	194	186
7	108	44	110	92	71	54	81	60	56	44	64	57
8	108	90	134	108	65	79	92	65	178	143	194	175
9	116	80	140	120	210	120	258	104	178	110	223	99
10	152	100	160	136	131	122	134	116	98	83	97	84
11	152	54	204	152	185	160	370	240	95	80	200	100
Average...	131.2	65.1	156.1	123.1	118.3	115.8	171.1	113.4	119.5	110.3	158.0	109.7
Experiments with the jugular veins ligated												
12	150	124	196	160	203	205	309	225	190	196	286	210
13	114	100	118	112	123	99	119	110	168	156	167	155
14	130	96	140	124	201	146	213	189	148	84	160	139
Average...	131.3	106.6	151.3	132.0	175.6	146.6	213.6	174.6	168.6	145.3	204.3	168.0

1 = early.
2 = late effects of the drug.

Experiments: The results upon the cerebrospinal fluid pressure are shown by table 25, which gives the results obtained from fourteen injections into dogs. A typical graph is shown in figure 29.

As can be seen from the table there may be in some a preliminary slight fall in venous pressure during the early stages of the action of a moderate dose of the drug, but this gives place to a marked rise in ve-

nous pressure during the depressor phase of the action of the drug. (See fig. 29.) The venous rise decreases, but persists during the arterial rise which follows the typical moderate dose, and then falls along with the arterial pressure. The fluid pressure follows the venous by the

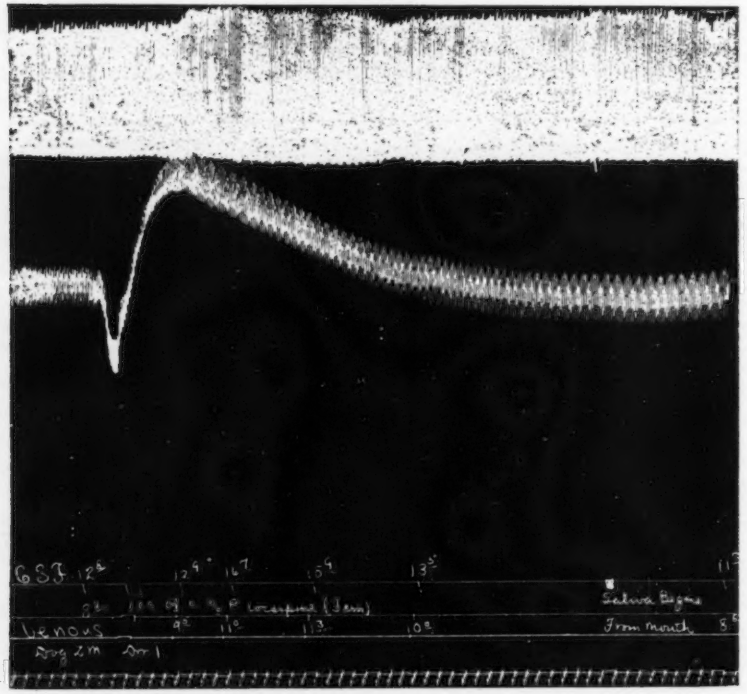

Fig. 29. This figure shows the effect on arterial, venous and fluid pressures of the injection of a small dose of pilocarpine. Note the parallel rise from the first of venous and fluid pressure. The arterial pressure fell, then rose, and then returned to normal.

manometer method. This is the usual result, and thus during the period of increased venous pressure, although arterial pressure is less than normal, an outflow fluid can be expected in the typical case. Anyone who has worked on the fluid is fully aware of the fact that the outflow does not always appear.

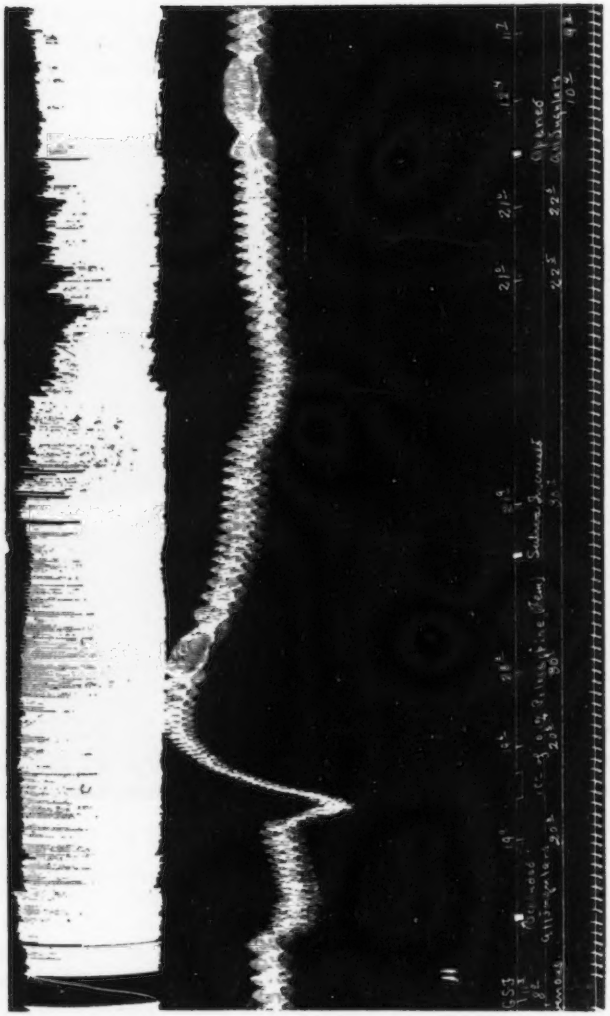

Fig. 30. This figure is from the same dog as figure 29. Conditions are exactly as in that figure except that the jugular veins were ligated. Note that the results are the same. Both cerebrospinal and venous pressures return practically to the secondary normal.

A glance at figure 31 shows what occurs in these cases. Where the dose is large, or the animal is especially susceptible to the action of the drug, a marked fall in venous pressure occurs, a fall which is paralleled by a decrease in fluid pressure. The cerebral venous and fluid pressures rise synchronously later after the cardiac depression has passed off.

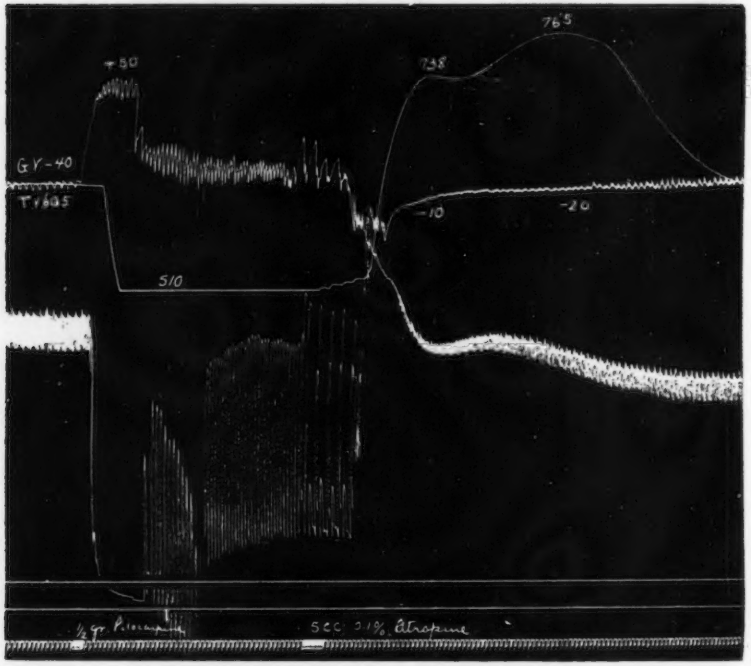

Fig. 31. This figure shows the effect of a large dose of pilocarpine, with powerful vagus inhibition. Note that torcular pressure fell while general venous pressure rose. The total fall in torcular venous pressure is not recorded owing to the rubber coming in contact with the bottom of the tambour.

Since the primary action in the case of pilocarpine is due to the vagus stimulation, any result described under the action of the peripheral vagus may be seen early in the action of pilocarpine. The later action may be markedly different, depending on the action of the drug on the vasomotor center.

Naturally since we hold that the fluid pressure is so markedly influenced by venous pressure, and since alterations in the venous pressure are sufficient to explain all the changes in the fluid pressure we are of the opinion that stimulation of the secretory mechanism need not be assumed to explain all the changes in pressures following the administration of pilocarpine.

On this point we agree with Dixon and Halliburton's first statement regarding the action of pilocarpine on fluid formation. If it be granted —and it is undoubtedly true—that arterial blood pressure does influence the fluid pressure very markedly in some animals, not at all in others, another explanation of these authors' figure 19 is that the preliminary fall in fluid pressure was due to the fall in arterial pressure in spite of the rise in venous; the rise in fluid pressure was due to the rise in arterial in spite of and not because of the fall in venous. However, we saw no changes of this type in our many experiments. In our experience fluid and venous pressures run uniformly parallel. In some cases they varied with, and in others against the arterial pressure. That torcular pressure does not always rise with marked cardiac inhibition—as they assume always to be the case—is seen clearly in figure 31.

If further evidence is needed to prove this point we offer the following evidence: In table 25 it will be noted that in experiments 12, 13 and 14 the results are in no way different from those seen in the preceding eleven experiments. The pressures fell, then rose above normal, and then returned to or below normal. The same period of time elapsed in these that elapsed in the earlier experiments. Yet these were made on animals with the jugular ligated. If new fluid were formed under the influence of pilocarpine the result logically to be expected under the conditions of the experiment would be a delay of the return of the fluid pressure to normal until after the veins were released, for all the modern work tends to show that absorption is along the vein. As can be seen from the table and by comparison of figure 29 with figure 30, both of which are from the same dog, it can be seen that the curves of pressure were exactly the same whether the jugulars were or were not ligated before the experiment. As can be seen from figure 30, the ligation of the jugulars produced an initial rise in both pressures, the pilocarpine curve was then superimposed upon this rise, the pressures returned to the new normal in the normal time and then returned to near the original normal when the veins were released. It is thus perfectly obvious that all the changes to be observed in the behavior of the cerebrospinal fluid find an explanation in the mechanical

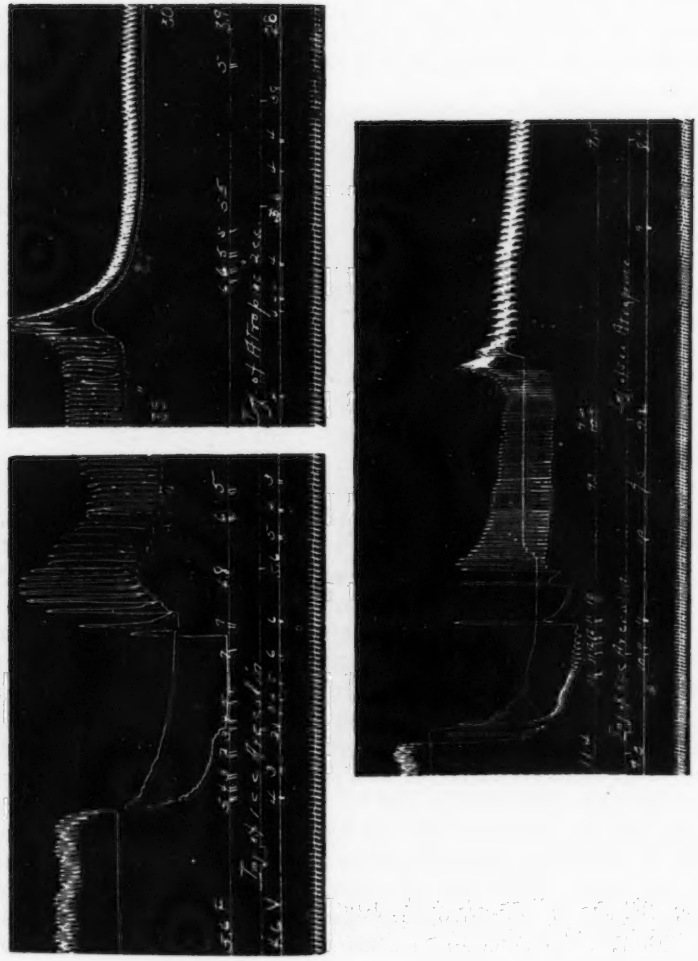

Fig. 32. This figure shows the effect of arecoline on all the pressures.

changes due to changes in arterial and venous pressure in the skull. Not only is there no need of ascribing the changes to secretion but there is positive evidence *against* the secretion of cerebrospinal fluid under the influence of pilocarpine. We believe that changes in the venous and arterial pressure are sufficient to explain the changes seen in fluid pressure and in fluid outflow when pilocarpine was injected.

b. Arecoline. Arecoline produces the changes to be expected if these changes are due to purely mechanical causes (see fig. 32).

c. Nicotine. Nicotine also produces changes which can be explained on a purely mechanical basis. (See fig. 33).

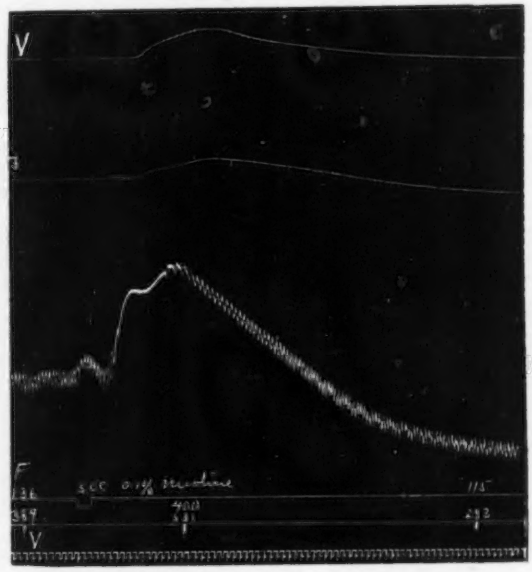

Fig. 33. This figure shows the effect of nicotine on all the pressures.

Drugs inhibiting the secretion of glandular organs

a. Atropine. Yoshimura (35) found microscopic changes in the choroid which he interpreted as the inhibition of fluid formation. Dixon and Halliburton (11) found with atropine an increased outflow especially if the drug was given soon after tapping the ventricle. This drug they classed among those yielding a slight increase in fluid formation.

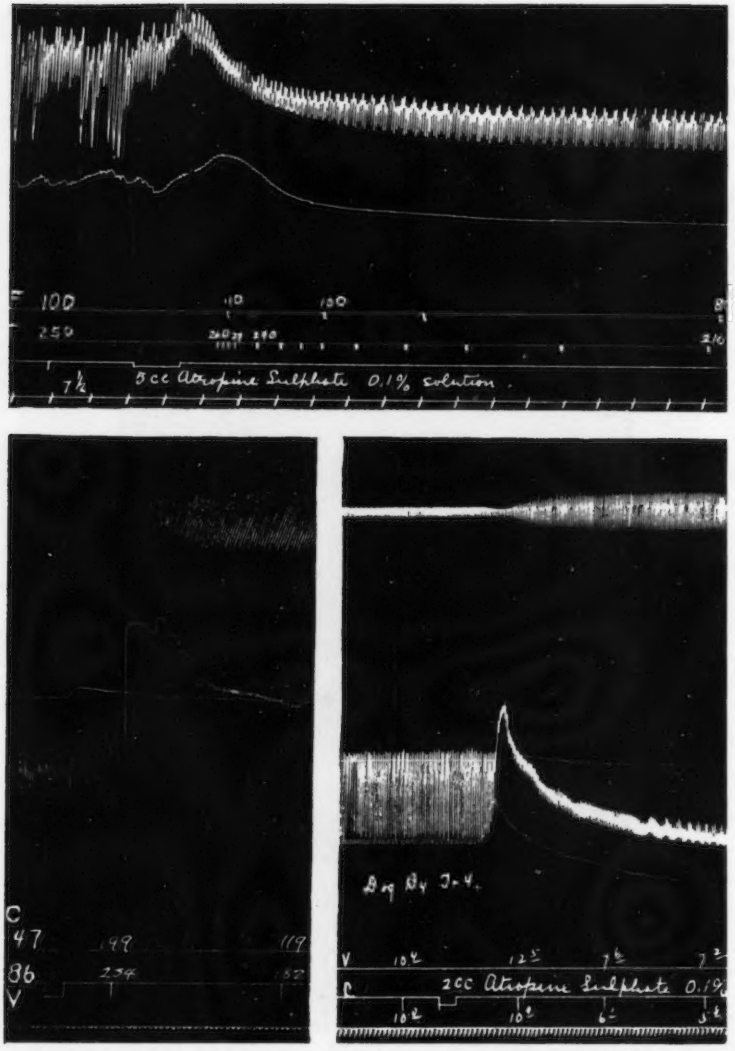

Fig. 34. This figure shows the effect of atropine on the various pressures. In each case a dose of pilocarpine had been administered previously.

Our experience with atropine is that the result is exactly what is to be expected from the alteration in the venous and arterial pressures. (See fig. 33.)

TABLE 26

This table shows the effect of the injection of amyl nitrite upon the arterial, venous and fluid pressures. It shows also the effect of the drug upon the outflow of fluid, and the arterial and venous pressures

	ARTERIAL			VENOUS			CEREBROSPINAL FLUID		
	B	D	A	B	D	A	B	D	A
1	130	96	132	78	73 89*	69	109	102 108*	76
2	170	136	168	140	125 155*	146	200	175 214*	208
3	168	104	156	136	110 140*	131	200	155 204*	195
4	144	100	154	141	135 150*	152	195	174 241*	247
5	144	198	150	560	365	520	385	245	387
6	120	70	114	76	54	69	211	120	226
7	96	56	88	59	49	53	66	52	56
8	164	86	122	87	80	72	216	164	205
9	144	120	144	96	85	98	124	109	120
10	124	58	80	148	84	127	145	105	138
Average.....	140.4	102.4	130.8	152.1	116.0	143.7	185.1	140.1	185.8

Outflow method

							Drops per minute		
1	96	44	108	86	80	85	4.5	0	0
2	108	54	110	88	82	85	2	1	2
3	126	92	120	205	186	200	5	0	1
4	164	130	170	153	129	154	2	1	2
5	158	114	166	120	100 128*	120	3	0 6*	2—
6	116	80	40	566	500	579	1—	19	1—
7	180	140	180	136	120	136	5	5	3
8	120	60	110	220	192	208	0	20	0
9	110	56	100	208	192	200	0	21	0
10	140	98	130	421	397	412	0	0	0
11	118	96	110	468	440	462	42	6	30
Average.....	130.5	87.6	122.2	242.8	219.8	240.1	5.8	6.6	3.7

* In these cases a secondary pressor effect followed the primary depressor effect, and showed itself clearly in both the venous and fluid apparatus.

Drugs having no effect on the secretion of glandular organs

a. Amyl Nitrite. As is well known amyl nitrite is an active vasodilator, and as such might be expected to produce rather marked effects upon the fluid pressures.

Dixon and Halliburton (11) in their first paper ascribed to amyl nitrite a slight stimulating action upon the mechanism generating the fluid. They believed that this effect was produced largely by asphyxia. In their second paper these same authors state (p. 151): "The rise in C-S pressure has certainly all the characteristics of an independent

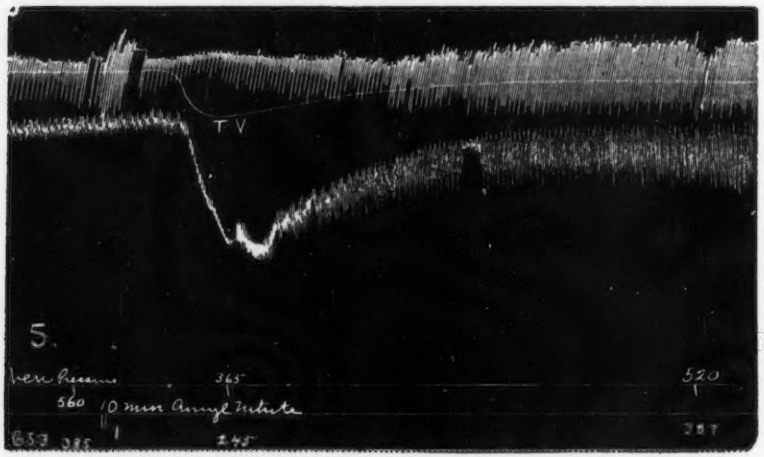

Fig. 35. This figure shows the effect on all the pressures of the injection of amyl nitrite. Note that all pressures fell.

factor," which we interpret to mean that they believe fluid formation to be stimulated by the drug. They show a tracing in which the rise in fluid pressure was large out of all proportion to the rise in venous pressure. At the same time the arterial pressure fell.

In table 26 we show our results in ten experiments by the manometer method, and in eleven experiments by the outflow method. Graphs of typical experiments are shown in figures 35 and 36.

As can be seen from our tables and figures, the effects of amyl nitrite on venous pressure are, in our experience, by no means the effects shown by Dixon and Halliburton. They state: "This effect (increased fluid

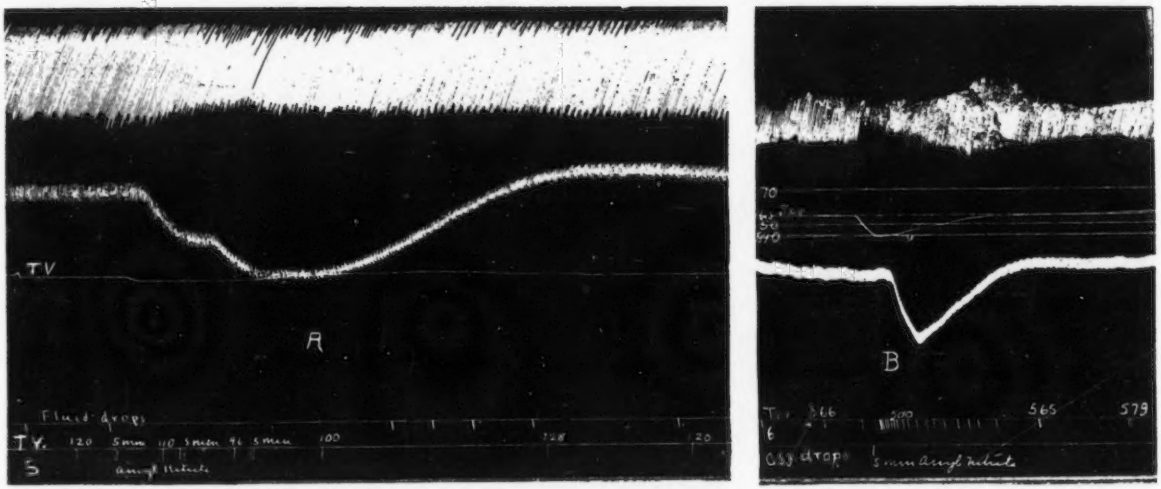

Fig. 36. This shows the differences in the reaction of different animals to the same drug, amyl nitrite. In both cases there was a fall in both arterial and venous pressures; while in *A* there was an almost complete cessation of the drops of fluid, in *B* there was a marked increase in the rate of flow.

outflow) is often associated with a general rise in venous pressure including torcular pressure." In *every one* of the twenty-one cases which we show in our table there was a fall in torcular pressure. In five of the twenty-one there was a secondary rise above the normal. It is to be noted also that in our table the fluid pressure ran parallel with the venous pressure. Sometimes it was higher, sometimes lower, but always it ran a parallel course. In those four cases where the venous pressure showed a secondary maximum after the fall the fluid showed a similar maximum above the normal. So much for the pressure method.

If we turn now to the outflow method it will be noted that in only four cases of eleven was there an increase in the outflow of fluid on the injection of amyl nitrite. In one of these (5) the increase was preceded by temporary decrease. The decreased outflow occurred during decreased venous pressure. It must be pointed out that an increase comes frequently by this method with both venous and arterial pressures below normal. (See expers. 6, 8 and 9, table 26, and fig. 36.) How there can be an increased ouflow with falling arterial and venous pressure has already been explained. The increased outflow is due to increased leakage of fluid from the cerebral cavity into the medullary region.

Our conclusion regarding the action of amyl nitrite is that all the changes observed in the behavior of the fluid can be explained logically by changes in arterial and venous pressure. Secretion need not be assumed to explain any of the facts.

CONCLUSIONS

1. The manometer method is superior to the outflow method as a means for studying the cerebrospinal fluid.

2. It is essential that arterial, venous and fluid pressures be measured simultaneously and continuously, if trustworthy evidence regarding the mechanism of fluid formation is to be obtained.

3. Venous and fluid pressures, while positive in normal animals, are always less than arterial pressure. Venous and fluid pressures are almost, but not exactly equal; no law can be given in regard to which is under the greater pressure.

4. Venous and fluid pressure vary in the same direction, and to some degree proportionally in nearly every case; these pressures may or may not vary in the same direction as the arterial pressure.

5. Raising the venous pressure raises the fluid pressure; lowering the venous pressure lowers the fluid pressure. Therefore the measurement of the venous pressure is absolutely necessary to rule out venous pressure changes, where the study of the fluid is under consideration.

6. Increasing or decreasing the fluid pressure moderately does not alter the venous pressure unless the arterial pressure is affected.

7. Ligation of the arteries entering the circle of Willis produces only passive changes in the skull characterized by a fall in the arterial, venous and fluid pressures, with almost perfect readjustment when the vessels are released.

8. Ligation of arteries in other parts of the body produces only mechanical changes.

9. The administration of adrenalin produces purely passive changes in the fluid pressure, although rapid outflow follows such an injection if the outflow method of study is employed. The fact that ligation of the jugulars does not modify the results either as regards the form or the duration of the curves of pressure change, is additional evidence that there is no new formation.

10. Arterial pressure can modify the fluid pressure independent of the venous pressure.

11. The fluid pressure is the result of at least two factors: The influence of the venous pressure, plus the influence of the arterial pressure; thus the fluid pressure in some animals will be higher than the venous pressure.

12. The effect of the peripheral vagus upon the fluid pressure is exactly what is to be expected, if the changes are due to mechanical causes. Increased secretion due to asphyxia need not be assumed to explain the results.

13. The greater the amount of fluid there is in the canal the more nearly does the fluid rise and fall equal the venous rise and fall following adrenalin; hence the animal with a large amount of fluid in the canal will show greater alterations in the fluid pressure during an experiment.

14. Increasing the active respiratory movements by stimulation of a sensory nerve like the sciatic, produces the changes in the fluid pressure to be expected from the changes in arterial and venous pressure. The same stimulation may produce either increased or decreased outflow of fluid, with the former the more common.

15. Inhibiting the respiratory movements by stimulation of the superior laryngeal or the central vagus raises the fluid pressure; but this

rise is adequately explained by the changes in the arterial and venous pressures.

16. The increased outflow of fluid observed during asphyxia is adequately explained by the rise in the arterial and venous pressures.

17. We were unable to reach any conclusions regarding the normal rate of the formation of the cerebrospinal fluid.

18. Adrenalin and nicotine are not absorbed from the canal rapidly enough to produce the characteristic effect upon the blood pressure.

19. Adrenalin can be detected in the canal for at least five hours after its injection.

20. Adrenalin is more rapidly destroyed *in vitro* by cerebrospinal fluid than by blood. A peculiarity in the reaction is seen in the fact that small quantities of the fluid, whether diluted or not, destroy adrenalin in solution more rapidly than do larger quantities of the fluid. This "protective action" of the larger quantity but not the destructive principle is destroyed by heating the fluid to 65°–75° for 30 minutes.

21. Secretin has no effect upon the pancreas when injected intradurally.

22. The effect of pilocarpine, when injected intravenously, upon the fluid can be explained logically by the effect of the drug upon the arterial and venous pressure in the skull. The same holds true for nicotine and arecoline.

23. The effect of atropine upon the fluid pressure can be explained logically by the effect of the drug upon the arterial and venous pressure in the skull.

24. Amyl nitrite always (twenty-one consecutive trials) produces a fall of the fluid venous and arterial pressures. The increased outflow of fluid, occasionally but by no means always observed, is due either to the accumulation at the expense of the fluid of venous blood in the sinuses with decreased venous pressure, or is due to the increased facility with which fluid passes into the region of the fourth ventricle from distant parts of the nervous system.

25. All the changes in the fluid pressure and fluid outflow which have been offered as proof of the secretory mechanism of formation of the cerebrospinal fluids can be traced to alterations in venous and arterial pressures in the skull. There is no proof that the fluid is formed by secretion.

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STUDIES ON THE CEREBROSPINAL FLUID

F. C. BECHT AND P. M. MATILL

From Northwestern University Medical School, Chicago, and from the Hull Physiological Laboratory, The University of Chicago

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VI. A STUDY OF THE EFFECTS OF TISSUE EXTRACTS

This series of experiments was undertaken with the view of determining what effect the injection of tissue extracts has on the cerebrospinal fluid and, particularly, to ascertain whether or not they possess a specific stimulating action, producing an actual increase in the amount of fluid produced.

It is an established fact that all tissue extracts—excepting adrenal and posterior lobe of the hypophysis—have a depressor effect on the vascular system. The amount of the depressor effect varies with the extract used—in general the extract of those organs having the largest external secretion produce the most marked effect (1). There is one exception—the extracts of nervous tissue give as decided an effect as any. In addition to the vascular effect, a number of recent workers claim a specific and direct action for certain of the extracts in causing an increase in the amount of cerebrospinal fluid, presumably by stimulation of the choroid plexus. Frazier and Peet (2) state that brain extract increases the secretion and that thyroid extract decreases the secretion from the choroid plexus, quite independent of blood pressure changes. Weed and Cushing (3) conclude that the extract from the posterior lobe of the hypophysis stimulates the choroid plexus, producing what they term a "choroidorrhea." Dixon and Halliburton (4), (5) conclude from their work that extracts from brain, and particularly from choroid plexus, cause a decided increase in the secretion of the fluid.

METHODS

In a previous paper (6) it has been pointed out that the conclusions set forth by these writers are open to criticism because with the methods employed, their observations were incomplete and thus subject to gross

error. In this series of experiments the manometer method, previously described, was employed throughout, the outflow method was employed only a few times to correlate our results with those of other writers. Particular care was observed in establishing venous and fluid pressures and if either of these was unsatisfactory the experiment was discarded. The circle of Willis pressure was taken in addition to the general arterial pressure but this worked well only in the larger dogs. All injections were made into the femoral vein.

Preparation of organ extracts. The organs and tissues used in these experiments were taken principally from dogs. The fresh tissues were removed promptly from the animal and if not used immediately were kept in the ice box. They were cut into small pieces and then thoroughly ground in a mortar with fine sand, and after being allowed to extract for about one-half hour, with either Ringer's or isotonic salt solution, they were centrifugalized. They were warmed before injection. Most of the extracts were made up to 50 per cent strength. The amount of tissue in the choroid plexus and in the hypophysis was so small that these extracts were made up so one cubic centimeter represented each choroid and each hypophysis. Aqueous humor and cerebrospinal fluid were taken at the same time that the choroid plexus and hypophysis were removed from the dogs—these fluids were used without concentration. Extracts were made of the following tissues: lymph gland, ovary, testicle, spleen, pancreas, submaxillary and parotid glands, skeletal muscle, heart muscle, kidney, liver, nervous tissue—cerebrum, cerebellum, medulla, cord and pineal body—thyroid gland, adrenal, hypophysis and choroid plexus. In addition a number of lymphogogues—urea, peptone, cane sugar and strawberry extract—were used.

For the sake of convenience in discussion and for the sake of brevity the extracts will be considered in three groups: *a*, those having a depressor effect on the vascular system—including those in which the effect was practically negligible; *b*, those having a pressor effect; and *c*, those for which a specific action is claimed, so modifying the activity of the choroid plexus that either an increased or decreased formation of the fluid results.

A careful tabulation was made of the principal changes in all the pressures caused by each of the extracts used, and thus the action of any one of them can be seen by reference to the proper table. Only three readings were recorded in the tables, though many more were taken. The first reading represents the normal pressure before injec-

tion, the second the maximum change after the injection, and the third represents the return to equilibrium. Where the changes in the arterial pressure were marked, the changes in the venous and the fluid pressures were practically always in the same direction though not exactly synchronous as to point of time—the maximum change in the latter being seen only thirty seconds to forty seconds later than the maximum change in the arterial pressure. The reason for this delay has already been discussed adequately (6). In a considerable number of cases there was an immediate and temporary rise in the arterial pressure following the injection, amounting usually to $2\frac{1}{2}$ mm.—this was usually accompanied by a corresponding rise in venous and fluid pressures. Since these vascular changes were not constant, it was thought best to omit them from the tables—reference will however be made to them later.

EXTRACTS HAVING A DEPRESSOR EFFECT

The list of extracts having a depressor or a negligible effect includes those made from spleen, pancreas, lymph-node, ovary, testicle, submaxillary, parotid, skeletal muscle, heart muscle, kidney, liver, also fluid and aqueous humor. Thyroid, choroid plexus and brain extract likewise have a depressor action, but for reasons already stated, viz., because a specific action has been ascribed to them by some recent writers, they will be discussed separately. A study of the tables, table 1 to table 3 inclusive, shows that all of these extracts produce very similar changes—the difference being a quantitative one only. Hence the effects produced by only one of these—kidney—will be taken as representative of the entire group, and it only will be discussed in detail. The results from other extracts are shown in the tables.

Effect of kidney extract on arterial, venous and fluid pressures. Five injections of 5 cc. each were made of kidney extract into four different dogs. Two injections were made in one experiment and the changes produced ran practically parallel in all the pressure tubes. The first injection caused a fall of 34 mm. of mercury and of 30 mm. in circle of Willis pressure (see exper. 3). In venous pressure there was a fall of 6 mm. (Na_2CO_3—1.088 sp. g.) and in fluid pressure a fall of 6 mm. (NaCl—sp. g. 1.088). All the pressures then rose and after they were again stationary the arterial pressures stood respectively 6 mm. and 4 mm. higher, and the cerebrospinal fluid and venous pressure stood respectively 7 mm. and 23 mm. higher than the normal before the

injection. The depressor effect of the second injection was slightly more than for the first—the fall in arterial pressures being respectively 44 and 36 mm. while the fall in venous and cerebrospinal fluid pressures were respectively 25 and 11 mm. (see exper. 2 and fig. 1). Here the recoveries were, with the exception of circle of Willis pressure, to

TABLE 1

Extracts of kidney, ovary, testicle

EXPERIMENT	Arterial			CIRCLE OF WILLIS			TORCULAR VENOUS			CEREBROSPINAL FLUID		
	B	D	A	B	D	A	B	D	A	B	D	A
1. Kidney extract												
1	160	102	168				94	76	112	122	112	142
2	120	76	120	82	46	78	127	102	127	79	68	79
3	116	82	122	78	48	82	82	76	105	68	62	75
4	136	118	150	130	116	138	67	65	61	48	47	46
5	122	88	130	107	80	115	109	79	118	132	109	144
Average	130.8	93.2	138	99.2	72.5	103.2	95.8	79.6	104.6	89.8	79.6	97.2
2. Ovary extract												
1	122	90	132	96	66	104	50	50	54	47	49	47
2	130	96	132	104	70	104	54	60	57	48	49	49
3	156	158	160	126	127	128	111	118	124	115	120	129
4	160	158	160				124	127	122	129	131	122
5	158	143	160	142	126	140	68	69	64	48	55	49
6	126	120	118	76	73	70	251	243	241	245	236	235
7	118	112	114	70	64	66	241	240	234	235	230	228
Average	138.5	125.3	139.4	102.3	87.6	102.0	128.4	129.5	128	123.8	124.2	122.7
3. Testicle extract												
1	154	114	146				87	65	71	116	102	105
2	112	104	108				88	87	87	94	92	91
3	104	94	104	80	80	80	77	75	78	288	278	288
4	104	96	104	80	70	81	78	66	65	288	252	255
Average	118.5	102	115.5	80	75	81.5	82.5	73.2	75.2	196.5	181	184.7

exactly the same levels as those preceding the injection. In experiment 1 the falls in pressures were again practically parallel—the fall in arterial pressure was comparatively larger than in experiment 2, and the changes in venous and cerebrospinal fluid comparatively less. These latter pressures stood higher after their return to normal than

they were before the injection but the final arterial pressure also stood higher than the initial one. The changes in experiment 5 were almost an exact repetition of those in experiment 1—there was a corresponding

TABLE 2

Extracts of liver, spleen, pancreas, submaxillary

EXPERIMENT	ARTERIAL			CIRCLE OF WILLIS			TORCULAR VENOUS			CEREBROSPINAL FLUID		
	B	D	A	B	D	A	B	D	A	B	D	A
4. Liver extract												
1	100	84	100	90	78	90	109	102	99	132	128	130
2	106	64	94	72	40	64	117	84	89	65	49	58
3	156	116	160				74	68	80	106	103	107
4	114	78	108	76	48	72	123	100	117	72	58	65
Average	119	85.5	115.5	79.3	55.3	75.3	105.7	88.5	96.2	93.7	84.5	90.0
5. Spleen extract												
1	148	146	158	142	140	142	66	69	69	45	51	49
2	130	112	122	115	102	110	118	114	88	144	122	97
3	166	100	148				110	73	88	140	108	123
Average	148	119.3	142.6	128.5	121	126	98.0	85.3	81.6	109.6	93.6	89.6
6. Pancreas extract												
1	130	86	128	89		84	96	80	90	61	46	60
2	106	76	110	84	48	74	119	70	71	79	38	41
3	100	54	74	90	48	68	99	52	78	130	105	111
4	160	70	130	128	76	120	130	70	91	115	80	65
5	144	76	78				89	47	45	126	88	87
Average	128	72.4	104	97.7	57.3	86.5	106.6	63.8	75	102.2	71.4	72.8
7. Submaxillary extract												
1	118	92	120	105	90	114	97	100	104	131	130	142
2	154	96	136				118	92	106	117	100	108
3	124	90	126	100	80	96	55	63	67	52	54	62
4	150	104	154	138	104	140	61	62	63	46	52	45
Average	136.5	95.5	134	114.3	91.3	117.0	82.7	79.2	85	86.7	84	90.2

fall in each of the pressures with a recovery in each case to pressures higher than the ones preceding the injection. In experiment 4 there was a slight fall in arterial pressure with practically no change in venous

TABLE 3

Extracts of lymph gland, parotid, skeletal muscle, heart muscle, peptone, urea and sugar solutions and strawberry

EXPERIMENT	ARTERIAL			CIRCLE OF WILLIS			TORCULAR VENOUS			CEREBROSPINAL FLUID		
	B	D	A	B	D	A	B	D	A	B	D	A
8. Lymph gland extract												
1	120	120	112				104	97	88	102	96	94
2	162	120	156				81	63	87	108	99	114
3	90	59	80	62	23	54	87	62	86	65	47	56
4	80	54	76	54	48	52	86	67	86	56	45	55
5	120	108	114	114	96	102	104	96	102	142	132	138
6	122	126	120	92	92	88	71	74	71	65	68	65
Average	115.6	97.8	109.6	80.5	64.7	74	88.8	76.5	86.6	89.6	80.8	87
9. Parotid extract												
1	137	80	124				105	83	107	106	82	104
2	90	58	110	52	56	86	67	60	90	189	129	245
Average	113.5	69.0	117				86	71.5	98.5	147.5	105.5	174.5
10. Skeletal muscle extract												
1	122	88	124	104	80	108	111	81	109	138	108	127
2	147	130	144				86	82	89	124	124	126
3	88	64	78	54	45	54	84	74	79	55	50	53
4	78	62	78	54	42	53	79	69	75	53	49	51
5	156	150	156	142	138	144	65	68	66	42	47	45
Average	118.2	98.8	116.0	88.5	76.2	89.7	85.0	74.8	83.6	82.4	75.6	80.4
11. Heart muscle extract												
1	112	130	120	92	102	98	110	132	119	122	142	141
2	120	114	122	99	94	104	113	102	111	141	129	138
3	120	72	122	94	58	96	98	83	105	243	170	268
Average	117.3	105.3	121.3	95.0	84.6	99.3	107.0	105.6	101.6	168.6	147.0	182.3
12. Peptone solution												
1	90	54	66	78	44	50	67	38	45	105	69	87
2	88	56	84				95	77	97	96	58	62
3	110	90	70	92	80	60	72	60	58	43	36	30
4	150	154	152	122	126	126	54	54	55	56	58	55
5	152	120	94	126	100	80	55	55	62	55	100	75
6	142	18	66	132	72	80	59	−10	36	64	−10	40
7	82	68	86	82	78	82	44	40	46	49	46	56
Average	116.2	80.0	88.2	105.3	83.3	79.6	63.7	44.8	57	66.8	51	57.8

TABLE 3—*Concluded*

EXPERIMENT	ARTERIAL			CIRCLE OF WILLIS			TORCULAR VENOUS			CEREBROSPINAL FLUID		
	B	D	A	B	D	A	B	D	A	B	D	A
13. Urea solution												
1	110	102	106	84	78	78	82	86	88	168	173	190
14. Sugar solution												
1	118	112	120	88	84	96	112	112	112	305	295	265
15. Strawberry extract												
1	120	90	112	94	70	88	78	65	77	139	127	146

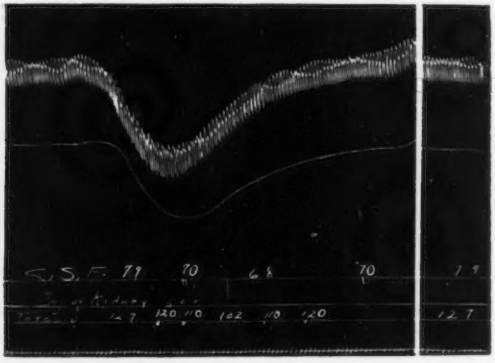


Fig. 1. This figure shows the effect of the injection of 5 cc. of kidney extract. Note the perfect return to normal of all the pressures.

and cerebrospinal fluid pressure; the final readings showed the arterial pressure to be higher and the venous and cerebrospinal fluid pressures lower than the normal pressures before the injection.

As has been stated, the changes produced by the injection of kidney extract on the fluid pressures are quite representative for all the depressor extracts. Throughout all the experiments, the correspondence between venous and cerebrospinal fluid pressure is especially to be noted. The changes are in the same direction and usually comparable in amount though never or rarely exactly equal. Where there is but little change in arterial pressure, as when aqueous humor is injected, there is little if any change in venous and fluid pressures.

However, in the vast majority of cases, where there is a marked fall in arterial pressure, there is a corresponding fall (see tables) in venous and fluid pressures. It has already been pointed out that the low points in the venous and fluid pressures are not reached synchronously with that in the arterial but follow the arterial fall by from thirty to forty seconds. The time at which the low points in venous and fluid pressure come depends largely on the change in the arterial pressure—if the arterial pressure rapidly returns to normal there is but a slight fall in

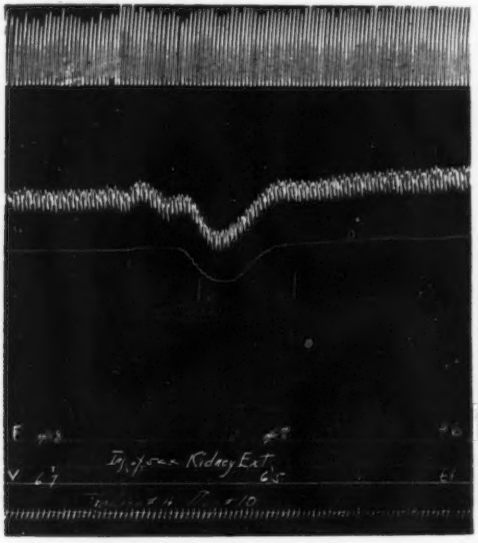


Fig. 2. This figure shows that when arterial drop and recovery occurs rapidly, the fluid and venous pressures may change together but do not follow the arterial change.

the venous and fluid pressures, following closely the change in arterial pressure; on the other hand, if the arterial pressure returns to normal slowly, then the low points in venous and fluid pressures are more marked and in point of time considerably later. In experiment 3, following the injection of 5 cc. submaxillary extract, there is a marked fall (see table 2) in arterial pressure with a return to normal in about thirty seconds. Here there is no fall in venous and fluid pressures—in fact these pressures show a very slight rise about thirty-five seconds

after the injection (fig. 3). In experiment 4, the injection of 5 cc. pancreas extract gave a decided fall in arterial pressure (see table 2) in which the return toward normal was very slow—here the lowest point in venous and fluid pressure was not reached for over two minutes. (See fig. 4). The experiments just cited are the exception rather than the rule—but they show clearly a fact which is not so evident in the average changes. The adjustment in the venous sinuses and fluid

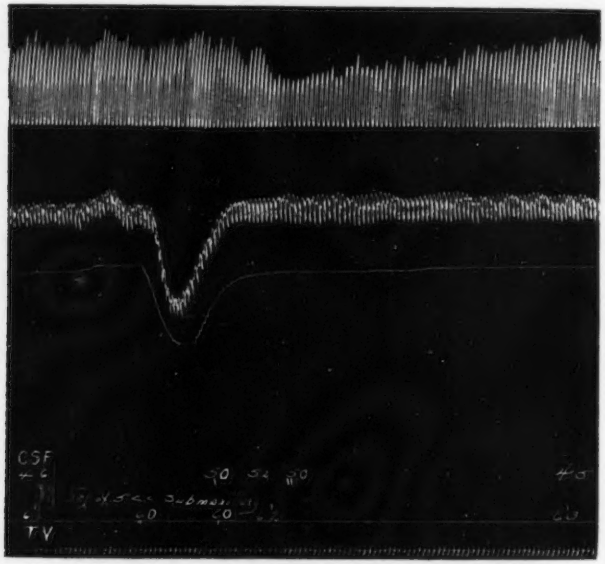


Fig. 3. This figure shows the effect of the injection of 5 cc. of submaxillary extract. Note that in this case the venous and fluid pressures rose with the fall in arterial pressure. This is different from the usual result.

spaces to changed arterial pressure is not immediate, probably because with each respiration there is a partial blocking of the various pathways of communication; hence when there is a fall in arterial pressure, some little time is required for the readjustment of the venous and fluid pressures. Thus if the return to normal is rapid as in experiment 4 (kidney, fig. 2) there is not sufficient time for readjustment in the venous and fluid pressures as there is in experiment 4 (pancreas, fig. 3) where the return to normal in arterial pressure is slow. Therefore it

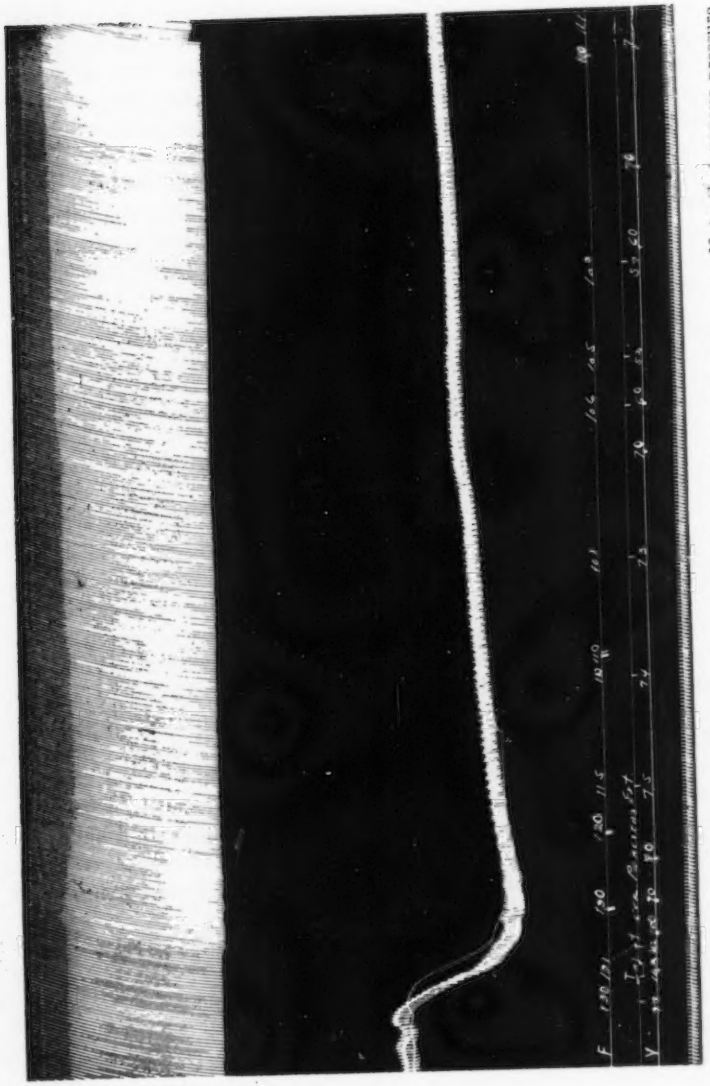


Fig. 4. This figure shows the effect of pancreas extract upon the various pressures. Note that venous pressure fell but made a fair recovery later.

is evident that the low point for venous and fluid pressures recorded in most of our experiments is not the low point which is possible with such a fall in arterial pressure since the arterial pressure commences to rise before sufficient time has elapsed to allow the venous and fluid pressures to become completely readjusted. These readjustments, which come slowly with a decrease in pressure, may show little if any delay with a rise in pressure, because the resistance offered to the redistribution of the fluid is readily overcome by increased pressure.

Our observations of the vascular and fluid changes following the injection of depressor extracts are directly opposite to those made by Frazier and Peet (2). They state (page 483):

> The administration of any depressor substance such as splenic extract, ether, amyl nitrate (?) or magnesium sulphate caused a marked drop in arterial blood pressure followed by a slow rise to normal. Practically coincident with the drop in arterial blood pressure was a sudden rise in cerebral sinus pressure. This usually occurred immediately after the sudden drop, and not with it. The sinus pressure continued to rise as long as the arterial pressure remained at its lower level. As the femoral pressure gradually returned to normal, the sinus pressure slowly dropped.

We do not doubt that such changes may occur—we observed a similar condition a few times (see figs. 3 and 12) but we do not agree that this is the usual change. Out of a total of about ninety injections of tissue extracts having a depressor action, we observed but a few well-marked instances of a condition which Frazier and Peet say is typical. (See table 6, line 8, and figs. 3 and 12). They do not state in how many animals the observations upon which they base their conclusions were made and in none of their tracings do they show a record of the venous changes recorded simultaneously with the arterial and fluid changes. Hence the conclusion must be drawn that their opinion was based on insufficient data, for in our paper we have recorded ninety simultaneous measurements of fluid and venous pressures, and of this number only a very few agree absolutely with what the authors mentioned consider typical.

As further proof for our contention that there is a very close correspondence between venous and fluid pressures, and that these in general follow the changes in the arterial pressures, we would refer the reader to figure 5 and to table 1 which show an average of all the pressure changes produced by kidney extract. It will be observed that for five injections there is an average fall in the general and circle of Willis arterial pressure of 38 and 27 mm. respectively, while in the venous

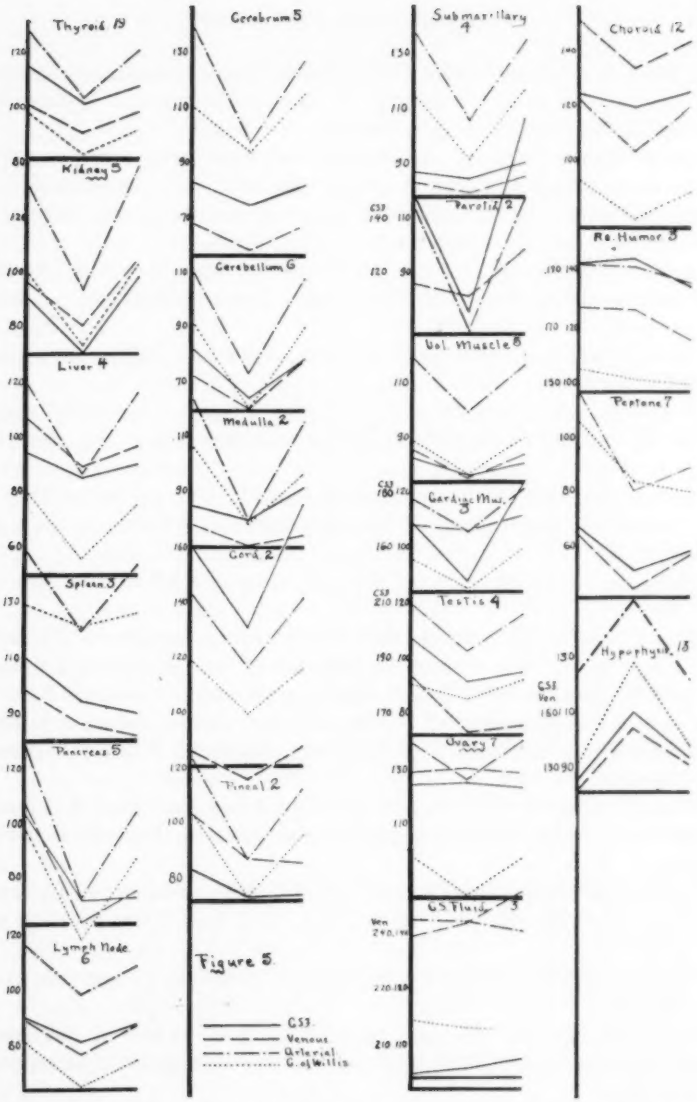


Fig. 5. This figure shows in diagrams the effect on all the pressures of all the tissue extracts. The figures are the averages of the pressures before, during and after the action of the extracts. The number of injections made in each case is indicated by the figure opposite the name of the tissue. Note the marked parallelism between venous and fluid pressures.

and fluid pressures there is an average fall of 10 and 16 mm. respectively. The average for the final readings of pressures shows each of them to be higher than the initial ones were.

If we study in detail the results obtained from extracts with a depressor action as shown in tables 1, 2 and 3, we must observe the following facts: In the case of ovarian extract considering only the average of seven experiments:

Arterial pressure fell 17.1 mm., then rose 18.0 mm.—a gain of 0.9 mm.

Circle of Willis pressure fell 13.9 mm., then rose 13.0 mm.—a loss of 0.9 mm.

Torcular venous pressure fell 18.6 mm., then rose 18.2 mm.—a loss of 0.4 mm.

Fluid pressure fell 19.4 mm., then rose 18.7 mm.—a loss of 0.7 mm.

In the case of testicular extract the averages of four experiments show:

Arterial pressure fell 16.5 mm., then rose 13.5 mm.—a loss of 3 mm.

Circle of Willis pressure fell 5.0 mm., then rose 6.5 mm.—a gain of 1.5 mm.

Torcular venous pressure fell 9.2 mm., then rose 2.0 mm.—a loss of 7.2 mm.

Fluid pressure fell 15.5 mm., then rose 3.75 mm.—a loss of 11.75 mm.

In the case of liver extract the averages of four experiments show:

Arterial pressure fell 33.5 mm., then rose 30 mm.—a loss of 3.5 mm.

Circle of Willis pressure fell 24 mm., then rose 20 mm.—a loss of 4 mm.

Torcular venous pressure fell 17.25 mm., then rose 7.75 mm.—a loss of 9.5 mm.

Fluid pressure fell 9.25 mm., then rose 5.5 mm.—a loss of 3.75 mm.

In the case of extract of the spleen the averages of three experiments show:

Arterial pressure fell 29.33 mm., then rose 24 mm.—a loss of 5.3 mm.

Circle of Willis pressure fell 7.5 mm., then rose 5 mm.—a loss of 2.5 mm.

Torcular venous pressure fell 9.3 mm., then fell 4.7 mm.—a loss of 14.0 mm.

Fluid pressure fell 14.7 mm., then fell 4.0 mm.—a loss of 18.7 mm.

In the case of extract of the pancreas the averages of five experiments show:

Arterial pressure fell 55.6 mm., then rose 31.6 mm.—a loss of 24 mm.

Circle of Willis pressure fell 40.45 mm., then rose 29.2 mm.—a loss of 11.25 mm.

Torcular venous pressure fell 42.8 mm., then rose 11.2 mm.—a loss of 31.6 mm.

Fluid pressure fell 30.8 mm., then rose 2.2 mm.—a loss of 28.6 mm.

In the case of submaxillary extract the averages of four experiments show:

Arterial pressure fell 41.0 mm., then rose 38.5 mm.—a loss of 2.5 mm.

Circle of Willis pressure fell 23.0 mm., then rose 25.3 mm.—a gain of 2.3 mm.

Torcular venous pressure fell 3.0 mm., then rose 5.75 mm.—a gain of 2.75 mm.

Fluid pressure fell 2.5 mm., then rose 5.25 mm.—a gain of 2.75 mm.

In the case of the parotid gland extract the averages of two experiments show:

Arterial pressure fell 44.5 mm., then rose 48.0 mm.—a gain of 3.5 mm.

Torcular venous pressure fell 14.5 mm., then rose 27 mm.—a gain of 12.5 mm.

Fluid pressure fell 42 mm., then rose 69 mm.—a gain of 27 mm.

In the case of lymph gland extract the averages of six experiments show:

Arterial pressure fell 17.8 mm., then rose 11.8 mm.—a loss of 6 mm.

Circle of Willis pressure fell 15.75 mm., then rose 9.25 mm.—a loss of 6.5 mm.

Torcular venous pressure fell 12.3 mm., then rose 10.1 mm.—a loss of 2.2 mm.

Fluid pressure fell 8.5 mm., then rose 5.9 mm.—a loss of 2.6 mm.

In the case of skeletal muscle the averages of five experiments show:

Arterial pressure fell 17.4 mm., then rose 35.2 mm.—a gain of 17.8 mm.

Circle of Willis pressure fell 12.3 mm., then rose 13.5 mm.—a gain of 1.2 mm.

Torcular venous pressure fell 10.2 mm., then rose 8.6 mm.—a loss of 1.6 mm.

Fluid pressure fell 6.8 mm., then rose 4.8 mm.—a loss of 2 mm.

In the case of cardiac muscle the averages of three experiments show:

Arterial pressure fell 16.5 mm., then rose 16.75 mm.—a gain of 0.25 mm.

Circle of Willis pressure fell 11.8 mm., then rose 14.3 mm.—a gain of 2.5 mm.

Torcular venous pressure fell 6.9 mm., then rose 7.8 mm.—a gain of 0.9 mm.

Fluid pressure fell 12.3 mm., then rose 16.3 mm.—a gain of 4 mm.

In the case of peptone solution the averages of seven experiments show:

Arterial pressure fell 36.2 mm., then rose 8.2 mm.—a loss of 28 mm.

Circle of Willis pressure fell 22.0 mm., then fell 4.0 mm.—a loss of 26 mm.

Torcular venous pressure fell 17.4 mm., then rose 10.8 mm.—a loss of 6.6 mm.

Fluid pressure fell 15.8 mm., then rose 6.8 mm.—a loss of 9.0 mm.

A study of the results of tables 1, 2 and 3 as just completed brings out convincingly the fact that in every case where there was a decrease in venous pressure there was at the same time a decrease in fluid pressure; when there was an increase in venous pressure there was at the same time an increase in fluid pressure. These pressures always vary in the same direction. If after the fall the venous pressure rose above the original level, as was the case in extracts of the kidney, submaxillary gland and parotid gland, and cardiac muscle, the level of the fluid rose above the original level; if after the fall the venous pressure remained below the original level during the period of observation, as was the case following the injection of extracts of ovary, testicle, liver, spleen, pancreas, lymph gland, skeletal muscle and peptone, the fluid remained below the original level. This parallelism certainly is more than a coincidence. Further, in one case, the spleen, the arterial pressure fell and then rose, but the venous pressure instead of rising as is ordinarily the case after depressor extracts continued to fall although the arterial pressure was rising. It will be noted that the fluid pressure continued to fall with the venous pressure rather than rising with the arterial pressure. Since it has already been shown that changing venous pressure by a moderate amount changes fluid pressure in the same direction, and to some degree proportionally, but changing the fluid pressure by less than 100 mm. of salt solution does not alter the venous pressure, it is evident that the determining factor for the fluid must be venous pressure and therefore the fluid pressure changes because of the changes in venous pressure. All the changes observed here can be explained readily on a mechanical basis and it is not necessary to invoke a theoretical increased or decreased activity of the mechanism producing the fluid in order to explain all the phenomena observed. The extracts when given intravenously produce certain changes in the venous pressure, and these changes in venous pressure determine the behavior of the fluid. This gives a purely mechanical explanation for the behavior of the fluid following the injection of tissue extracts. This is the conclu-

sion already reached by Frazier and Peet (2), although, as has been pointed out, their ideas regarding the behavior of the venous pressure are the opposite of those actually observed by us in practically every one of ninety injections of extracts of various organs. Experiments on other parts of the field (6) show that the behavior of venous pressure is the same no matter whether the manometer or the outflow method of studying the behavior of the fluid is employed.

This relationship between all the pressures, as shown by the averages of all of the injections of any one extract, serves to show what will be observed following injection of any depressor extract—namely, that the changes produced in the fluid are mechanical, and that they are dependent primarily on venous changes. Allowing for the error in the method employed, all the changes observed in the fluid following the injection of depressor extracts can be accounted for by the changes in the venous pressure. The venous pressure is, it is true, ultimately dependent upon the arterial pressure, but can and does undergo variations independent of arterial pressure, and while it has been shown that arterial pressure influences fluid pressure the chief influence is still by way of the venous pressure. Our series of experiments gives abundant evidence that arterial and venous changes do not necessarily run parallel (6), particularly where the changes are comparatively small. Therefore it will be seen that for any adequate interpretation of the changes taking place in the fluid pressure, it is absolutely necessary to know what changes are taking place simultaneously in the venous sinuses of the skull. General venous pressure elsewhere in the body has no bearing on this question, as was shown in an earlier paper.

The lymphagogues are in the same class as the extracts already discussed. The effect produced by them on the fluid pressure was in every way comparable to the changes produced by the tissue extracts, insofar as they produce any vascular effects. Peptone caused a decided fall in arterial pressure and consequently marked changes in the fluid pressure. Sugar caused little vascular change and therefore little change in the fluid pressure, showing that whatever the change, the result was purely mechanical.

How, then, if arterial and venous pressures both fall following the injection of most tissue extracts instead of the former falling and the latter rising as is stated by Frazier and Peet, can we explain the mechanism of increased outflow of fluid following the injection of these extracts? That the intravenous injection of these extracts produces an increased outflow of fluid at least temporarily is not to be doubted. In-

creased venous pressure, if such could be shown, would furnish the *vis a tergo*, but we have shown that venous pressure as well as fluid pressure falls instead of rising, so some other explanation must be sought. The changes recorded by Frazier and Peet are much greater than we secured with the animal on his side. As was pointed out, the position they used favored the escape of preformed fluid by making the point of drainage the lowest point in the system. We believe that using the outflow method, tissue extracts produce their effect by reducing arterial and venous pressure, thus shrinking the sinuses and permitting the fluid in the cerebral cavity, which up to this time has been prevented from passing the strait, at the region of the mid-brain, to pass into the region of the fourth ventricle and out through the needle. If this is true then dogs with no fluid over the cerebrum will give negative results. Any worker will testify that many animals fail to show an increase. One further possibility has been pointed out: If the resistance offered by the fluid in passing through the needle is less than that offered by the venous blood in passing by natural channels (veins) to the heart, then the amount of blood accumulating in the sinuses would increase at the expense of the fluid. The accumulation of blood would thus displace an equal amount of fluid, thus setting up a pseudo-secretion without a rise, or perhaps even with a fall of venous and fluid pressures. The conditions present in Frazier and Peet's experiments are almost ideal for this mechanism of outflow for the fluid has only to flow under the influence of gravity down the plane offered by the nervous system and meninges to escape. The graduated tube adjusted level offers some resistance but very little in the outward direction, and this little is easily overcome by the influence of gravity.

We are convinced that the effect of tissue extract upon fluid outflow is simply to facilitate the escape of preformed fluid, either by making the transit of fluid past the various straits easier or by producing a condition whereby venous blood accumulates in the skull at the expense of the fluid. This is the conclusion reached by Frazier and Peet in their study of the tissue extracts thus far reported, but our conception of the mechanism involved is different from theirs, theirs being founded upon the erroneous idea that venous pressure rises in the skull just after the fall in arterial pressure, whereas our work shows that venous pressure falls along with arterial in almost every case.

EXTRACTS HAVING A PRESSOR EFFECT

Extracts from the adrenal and from the posterior lobe of the hypophysis produced a pressor effect on the vascular system. Since hypophysis extract is claimed to have a specific action on the choroid plexus, (3) it will be discussed under the third group. Only a few extracts were made from the adrenals because the effect produced by the fresh extract was entirely comparable with that of the commercial preparation, but less active. Hence for additional data we refer the reader to the tables in another article (6), which give the changes produced by adrenalin chloride. The rise in arterial pressure following injection was accompanied by a corresponding rise in venous pressure and cerebrospinal fluid pressure, the fall in arterial pressure by parallel decline in venous and fluid pressures. The changes in the fluid pressure with adrenal extract are so obviously dependent on the vascular changes that workers are agreed that the changes are mechanical. Since the arterial changes, particularly after atropine, are usually very pronounced and continue for a relatively short time, a closer relationship is to be seen between arterial and fluid changes because the venous pressure follows the arterial more closely. Therefore, even though previous workers did not record venous pressure, they nevertheless arrived at the correct conclusion.

EXTRACTS SAID TO HAVE A SPECIFIC ACTION ON THE RATE OF FORMATION OF THE CEREBROSPINAL FLUID

Pressor extracts

Extracts of the pituitary and the adrenals. In accordance with the principles laid down in the earlier work, it is held that before it is necessary to ascribe an increased fluid pressure or an increased fluid outflow to an increased rate of formation of fluid, all of the physical factors capable of producing such change must be measured and shown to be unchanged, or altered in such manner as to produce a change opposite to that noted in the fluid. It has already been shown that alterations in the venous pressure invariably produce a change in the fluid pressure in the same direction and to some degree proportionally. Arterial pressure modifies the fluid pressure in some cases, but does not modify it in others, the determining factor being the amount of fluid in the canal: with a large amount of fluid in the canal the fluid pressure rises or falls with the arterial, with a small amount of fluid in the canal

the arterial pressure loses its effect because the dilatation and constriction in the artery are not sufficient to affect the fluid pressure, for all the force is carried by the arterial wall without much if any dilatation, and so the force is not transmitted to the fluid. The question of the change of pressure in the artery would not enter to any degree, if at all, in the outflow method, for most of the excess of fluid has escaped before the experiment is begun. It seems highly improbable that the alteration in the volume in the arterial side of the capillary due to increased arterial pressure will to any degree equal the amount of change produced by the dilatation of the vein produced by increased accumulation of blood in the sinuses by increased venous pressure. The influence of respiration has already been adequately discussed. It was shown to be variable, both as regards amount and character of change. Sometimes there is an increased, sometimes a decreased outflow, depending upon whether there was free or difficult communication between the various cavities, and as to whether there was much or little fluid stored in one of the cavities shut away from the *cisterna magna* by the position of the brain and medulla. Thus it becomes clear that it is absolutely necessary that venous and arterial pressure and the influence of respiration be measured in every case before the significance of the rise in fluid pressure, or the increase in the outflow can be properly estimated.

Applying this knowledge to the effects of the injection of extracts of the pituitary and of the adrenal upon the formation of fluid, it is necessary that a careful study of the behavior of all these pressures be made in order to ascertain whether anything more than pure mechanical factors are involved in the rise in the fluid pressure and the increased outflow of fluid from the canal after the injection of pituitary extract or adrenalin.

A survey of the recent literature shows that there are divergent opinions regarding the influence of extracts of the pituitary on the formation of the fluid. Weed and Cushing (3) conclude: "Extracts of the posterior lobe of the hypophysis increase the rate of production of cerebrospinal fluid (choroidorrhea) by stimulating the secretory activity of the choroid plexus." Dixon and Halliburton classify pituitary extract with substances producing "no increase or diminution" in outflow (p. 239). Later (5) they agree with Weed and Cushing that in animals breathing naturally, pituitary extracts produce an increased outflow of fluid, but assert that if the animal is deeply anesthetized and ventilated artificially, pituitary extracts produce no increased outflow. They ascribe the increased outflow seen in the normally breathing animal to asphyxia because of bronchial constriction.

Regarding the influence of adrenalin, Dixon and Halliburton state: "A sudden rise in arterial pressure such as is produced by adrenalin in dogs with cut vagi, will produce a mechanical pressing out of accumulated fluid." Earlier observers, particularly Spina (7), were of the opinion that adrenalin increased the fluid outflow by increasing the transudation through the pial vessels.

It is thus evident that there is a divergence of opinion in regard to the action of these drugs. We do not know whether or not there is an increase in the amount of fluid formed; or if there is an increase, whether the increase is due to accelerated secretion due to stimulation or increased transudation. If there is increased stimulation of the secretory mechanism, we do not know from the literature whether there is an active principle found in the pituitary stimulating the cells specifically or whether the extract of pituitary produces its effect indirectly by asphyxia. Granting for the time being the unification of views suggested by Dixon and Halliburton for the differences between their findings and those of Weed and Cushing, and thus granting that in the naturally breathing animal there is an increased formation of fluid as manifested by increased outflow by the outflow method, or increased pressure by the manometer method, an exhaustive study of the behavior of arterial, venous and fluid pressures must be made in order to rule out the possibility of the change being purely mechanical.

Regarding adrenalin Dixon and Halliburton say: "A sudden rise of arterial pressure, such as is produced in dogs with cut vagi, will produce a mechanical pressing out of accumulated fluid" (p. 239), a finding with which we agree absolutely.

Since pituitary and adrenal extracts both contain an arterial pressor substance, and since changes in arterial pressure produce so frequently changes in other parts of the vascular system, particularly in the venous circulation in the skull, which has already been shown markedly to influence the behavior of the fluid, the question naturally arises as to whether the assumption that pituitary extracts have a stimulating effect, while the adrenalin has only a mechanical effect upon the fluid, is logical.

Of course it is well known that there are some marked differences between the actions of adrenalin and extracts of the pituitary: Adrenalin has been shown (8) to stimulate the secretion of the salivary and lachrymal glands supposedly with increased circulation in the former (9) although secretion in most glands is depressed by the powerful vasoconstriction (10). Pituitary extracts are said to depress the secretion

of the submaxillary partly by vasoconstriction, partly by direct depression of the salivary cells (9). Thus it is clear according to the literature that adrenalin stimulates, extracts of the pituitary depress secretion of the salivary glands, exactly the opposite of the findings in the case of the cells forming the cerebrospinal fluid, where adrenalin has no effect and pituitary extract stimulates them to greater activity.

There is almost as much difference between the effects of these drugs upon blood pressure as upon salivary secretion: Adrenalin intravenously produces a rapid rise in the blood pressure which begins in three to ten seconds, reaches a maximum five to ten seconds later, and disappears in twenty seconds to two minutes. Except for the latent period all these phases are modified by the dose employed and by the action of the vagi. Pituitary extracts frequently produce a fall, and then a slow, long-continued rise. The former is not constant and may be due to some extraneous material in the preparation. The rise begins in less than a minute and lasts five to thirty minutes. Secondary rises after the first are not uncommon. The point of action as well as the character of the curves is different: both drugs act peripherally. Adrenalin is believed to act on the physiological sympathetic nerve endings. The physiological endings must be affected because the action of adrenalin is prevented or reversed by the previous action of apocodeine (11) and ergotoxine (12). If the point of action were the muscle, the reaction would be the same both before and after these drugs. Further Maass (13) has shown that the accelerator (sympathetic) nerves to the heart carry vasodilator fibers to the coronary arteries. Langendorff (14) has shown that the effect of adrenalin on the coronary area is dilatation, not constriction. These two facts are further support for the idea that adrenalin acts on the sympathetic endings and not on the muscular wall, for we have no reason to believe that the muscles of the coronary vessels differ essentially from those of other vessels. That the action of adrenalin does not depend upon the anatomical nerve endings is shown by the fact that the drug has a typical effect upon a part when the nerve endings have degenerated after section of the nerve (15). Pituitary extract acts upon the muscle of the wall for its effect is typical after apocodeine and ergotoxine. In addition to the points already discussed there is another marked difference between adrenal and pituitary extracts in their effects upon the blood pressure: Adrenalin not only produces its effect repeatedly, but almost quantitatively (16). Pituitary extracts produce practically no effect on a second injection immediately after the blood pressure has returned to normal after a

first injection. Some claim there may even be a reversal of the curve on repeated injections (17), others claim that the effect may be reproduced if the doses employed are small and the injection is not repeated until about a half or three-quarters of an hour has elapsed (18). Thus there are enough differences between the action of adrenalin and pituitary extract to warrant the belief that one might stimulate some cells to increased secretion, the other might produce increased outflow by purely mechanical means.

Under the belief that the truth regarding all the factors can be arrived at only by the study of rather a large number of cases, we undertook the work on a number of dogs. Using the manometric method, twelve injections of fresh extracts of dog pituitary were made into eleven dogs. Five were extracts of the entire organ, three were extracts of the anterior, four of the posterior lobes, four injections were made with proprietary preparations from various drug houses (table 4).

In experiment 1 the extract of the entire hypophysis of one dog was injected. There was first a pressor effect, and there were simultaneous rises in venous and fluid pressures. In experiment 2 a similar injection gave first a slight depressor, but later a pressor effect on arterial pressure. This rise may have been due in part to asphyxia, for the animal ceased breathing for a time. And here as before both venous and fluid pressures rose simultaneously. In experiment 3 the injection of 5 cc. of the extract gave an immediate pressor arterial effect followed by a long-continued high pressure. The rises in fluid and venous pressures were again simultaneous and practically equal in amount. In all the experiments described the final pressure readings were all higher than the normal preceding the injection. In experiment 4 the injection of 5 cc. of extract of hypophysis produced a depressor arterial effect accompanied by a rise in venous and fluid pressures, here the final reading for arterial pressure was lower than the initial one, but the venous and fluid pressures were higher. It is well to note again at this point, as was done in the earlier paper, that arterial and venous pressures do not always run parallel. This is true after the injection of pituitary as well as for other extracts. This experiment is very similar to the results with choroid plexus extract in experiment 8 in which the high point of fluid and venous pressures came with the low point in arterial pressure (see fig. 12), and agrees with what Frazier and Peet believe to be the usual result with depressor extracts. A second injection of hypophysis extract in this same animal (exper. 5) gave practically opposite results. There was a slight pressor effect on arterial pressure accompanied by a

slight fall in venous and fluid pressures. The final readings in arterial pressure were slightly less than the initial pressure, while the venous and fluid pressures were practically the same. The variability shown in the two injections of the same extract, into the same animal, emphasizes again the importance of taking the venous pressure simultaneously with

TABLE 4

Extract of hypophysis

EXPERIMENT	ARTERIAL			CIRCLE OF WILLIS			TORCULAR VENOUS			CEREBROSPINAL FLUID		
	B	D	A	B	D	A	B	D	A	B	D	A
Entire hypophysis												
1	162	183	165	120	132	127	145	159	160	162	168	170
2	134	132	150				77	90	95	109	110	130
3	132	160	146	100	136	124	83	112	109	85	108	107
4	140	124	126				90	117	101	105	118	111
5	150	156	140				75	72	77	88	83	87
Posterior lobe extracts												
1	146	172	150	84	144	120	276	356	304	257	321	274
2	84	106	78	62	80	62	253	239	230	138	187	142
3	112	194	146	82	164	112	89	149	140	87	143	140
4	150	186	90	114	152	72	129	81	84	142	98	114
Commercial extracts of pituitary												
1	106	160	116				107	122	110	69	70	66
2	88	106	16				96	97	98	98	127	90
3	124	128	124	100	104	100	108	129	110	106	129	109
4	108	158	110	78	106	66	59	149	85	193	285	192
Average	125.8	151.1	119.7	92.5	127.2	97.9	122.1	144.0	131.0	126.0	149.7	133.2
Anterior lobe extracts												
1	152	154	156	118	119	119	309	315	321	282	288	296
2	124	118	128	92	94	104	111	103	91	153	148	138
3	72	82	88	54	54	66	241	270	262	124	140	105

the other pressures, for without knowing the changes taking place in the venous sinuses, the explanation of the changes in the fluid can be guesswork only.

Anterior lobe extracts. Extracts of anterior lobe were used in three experiments: Little vascular change was produced by these extracts

and the changes in arterial, venous and fluid pressures were all parallel. These changes in pressure were typical and are to be explained on a purely mechanical basis.

Posterior lobe extract. In experiment 12 the injection of 2 cc. posterior lobe extract gave immediate and long-continued pressor effect (see fig. 6). The venous and fluid pressures rose simultaneously with the arterial and the high point in all of them was reached at practically the same time. The fall in all the pressures was gradual but in every case the final readings were slightly higher than the initial ones. A study of the tracing will show the close relationship of all the pressures and particularly of the venous and fluid pressures. The comparatively greater rise in circle of Willis pressure as compared to general arterial pressure following the injection of posterior lobe extract is a striking feature of this tracing. This effect appears to be quite common after pituitary injections, but its significance is not understood. In experiment 2 the injection of 2 cc. posterior lobe extract gave an immediate though comparatively short pressor effect. There was a corresponding rise in fluid but little rise in venous pressure. The final reading showed the fluid pressure to be comparatively higher than either the venous or arterial. This might be interpreted as an actual increase in fluid due to secretion but we do not believe it is: this increase in fluid is the exception rather than the rule. It should appear more frequently than once in fourteen injections; further the same change is observed in the case of other extracts. See line 9 in table 7 showing the effect of thyroid injections. The increase is very small in amount (1 cm. on the manometer equals 0.03 cc.) and therefore after allowing for error in the method, the increase is negligible. Further we know that a rise in arterial pressure can produce a rise in fluid pressure.

In experiment 3 the injection of 4 cc. posterior lobe extract gave an immediate short pressor effect, followed by a long pressor effect. The high points were reached in the venous and fluid pressures before those in the arterial pressures. There was an immediate gradual parallel decline in venous and fluid pressures in spite of a decided second pressor arterial effect. The final arterial pressures were lower while the venous and fluid pressures were practically the same as at the first readings. This injection shows clearly the variations that are so often seen between arterial and venous pressures but at the same time it gives additional support to our contention that there is a close correspondence between venous and fluid pressures.

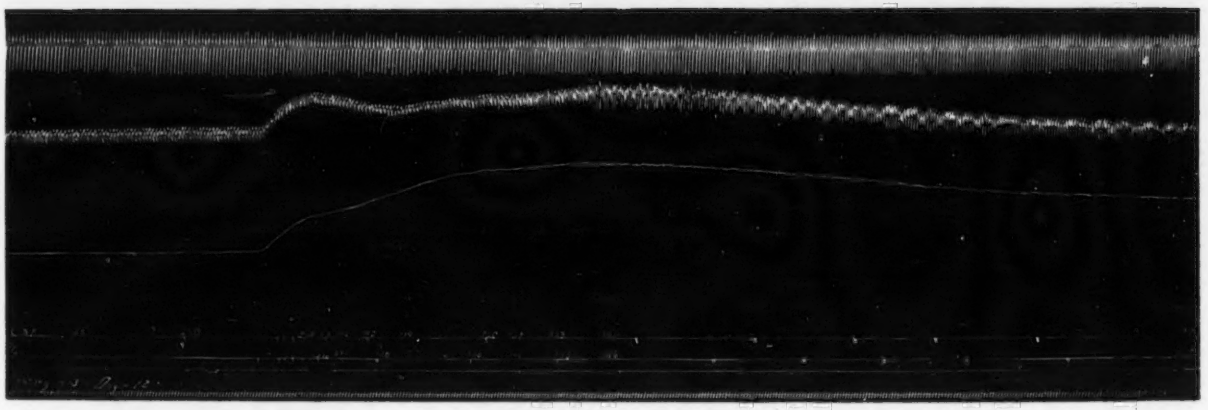


Fig. 6. This figure shows the effect of the injection of an extract of posterior lobe of the hypophysis. The pressure method of recording was employed. Note that all pressures had returned almost to normal by the time the tracing was discontinued. Complete readjustment was noted later.

Pituitary Liquid (Armour) was injected into a number of animals but the vascular changes produced were quite variable. In experiment 4 a marked and rather long-continued pressor effect was produced; the changes in the venous and fluid pressures were in the same direction as the arterial but comparatively smaller. Here the final pressures, with the exception of the fluid pressure, stood higher than the initial ones. This is in striking contrast to the observation in experiment 3 in which the fluid pressure was comparatively higher than the other pressures—if the one were called secretion, then the other with equal right could be called absorption.

A careful survey of the effects produced by the injection of pituitary extracts shows that although the pressor changes were of longer duration than those produced by adrenalin, nevertheless the fluid changes followed the vascular changes and in particular the venous changes, closely. With the single exception, noted above, in experiment 2 (posterior lobe extract) there was no evidence of a "choroidorrhea" such as is described by Weed and Cushing (3). In fact all of the changes observed can be accounted for by vascular changes, the most important of which are the venous pressure changes. That Weed and Cushing recognize the possibility of the fluid being affected by the venous pressure is shown by their own statement: "in view, therefore, of the possible influence of these physical factors on the discharge of the fluid, it is hazardous to assume that certain agents stimulate the secretion of the choroid plexus, merely because of an increased flow from a cannula." Had they measured venous pressure simultaneously with the arterial and respiratory changes, they would undoubtedly have observed one more of the physical factors concerned in the outflow of the fluid. They recorded the respiration but evidently did not regard it as significant—that it may be an important physical factor where the outflow method is employed has been clearly shown in a previous article (6). The amount of fluid in the subarachnoid spaces at the time of the injection and the limitation of the fluid pressure to the resistance of the cannula employed are other physical factors which they failed to consider at all.

The basis for their conclusion that the extract of the posterior lobe of the hypophysis produces a "choroidorrhea" is briefly stated as follows: *a*, that there was an actual secretion because there was no recession of fluid in the cannula; *b*, that the catheter was in the ventricle rather than the subarachnoid cistern; and *c*, the apparent fatigability of the response to repeated injections. The weakness of their first

and second arguments has already been pointed out clearly (6). Briefly they are as follows: *a*, the subarachnoid spaces are surrounded on the one hand by the undilatable calvarium and on the other by the relatively incompressible brain substance; hence little negative pressure could be developed to cause a recession of the fluid into the catheter or tube. Therefore, a lack of recession of fluid would mean nothing. *b*, The presence of the catheter in the ventricle does not eliminate the possibility of a transudation of the fluid from the capillaries, which under the experimental conditions might be greatly increased; neither does it eliminate the possibility of a backward flow through the aqueduct of Sylvius, unless the catheter is placed into the aqueduct. The weakness of their third argument lies in the fact previously stated, i.e., that a second injection of pituitrin produces little or no vascular effect. If the changes produced in the cerebrospinal fluid by the injection of pituitrin are mechanical, as we believe they are, then if a second injection produced little vascular change, a correspondingly small fluid change would be expected. Furthermore, if the preformed fluid were forced out to a considerable degree following the first injection, there would be little left to be forced out following a second injection. That the amount of fluid in the subarachnoid spaces is important in determining the outflow from the cannula has likewise been clearly shown in the previous paper. It would appear, therefore, that it is entirely unnecessary to assume that the cessation of flow is due to the fatigability of the choroid because this (cessation of outflow) can be satisfactorily explained by the physical factors involved.

The tracing presented by Weed and Cushing to prove that the outflow is independent of vascular changes is not complete. To compare with records I and II of their paper we show figure 7, a graph which reproduces almost exactly the arterial curve which they show. As can be seen from the readings of fluid and venous pressures on our curves, synchronous with the fall in arterial pressure there was a rise in venous pressure, a rise reaching a maximum of 28 mm. above normal. Almost simultaneously with the minimum of arterial pressure and synchronous with the rise in venous pressure was a rise in fluid pressure of 23 mm. Both venous and fluid pressures fell below normal as arterial pressure rose, and then rose to normal as arterial pressure reached its maximum. This rise in fluid and venous pressure came at about the time when there is in records I and II an increase in fluid outflow, and a rise in venous pressure is able to produce just such an outflow as is shown by the ligations of the jugulars shown in the preceding paper. We are con-

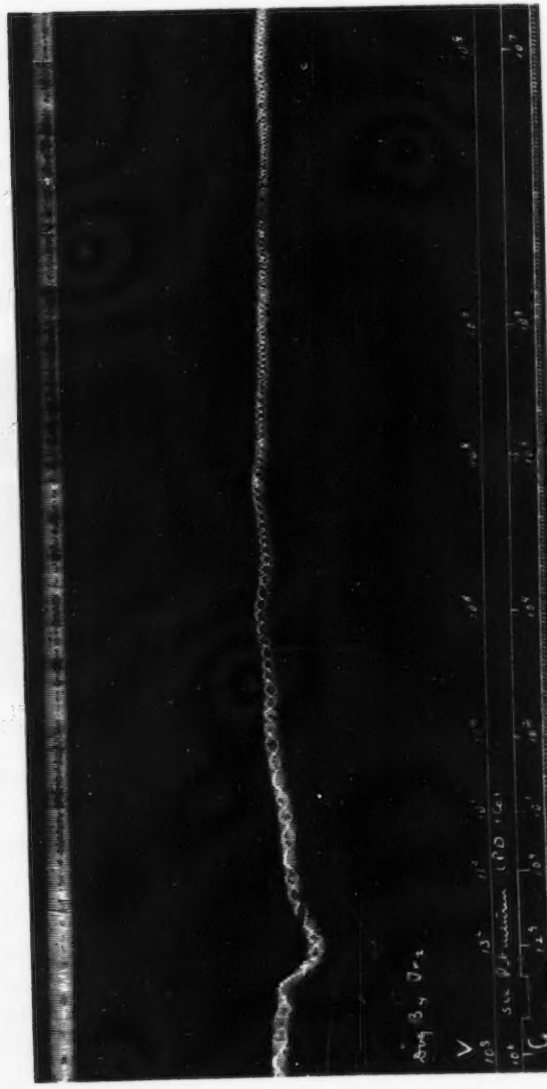


Fig. 7. This figure shows that with the preliminary fall in arterial pressure common soon after pituitrin injections there is frequently seen a marked rise in venous pressure with a corresponding rise in fluid pressure.

vinced that if the authors mentioned had had a venous tracing of the experiments shown in I and II they would have found a rise in venous pressure synchronous with their increased outflow. Figure 7 shows such a venous pressure rise with a simultaneous fluid pressure rise. Figure 8 shows a similar result where the outflow method was employed, a fall and then a rise in arterial pressure with a rise and then a fall in venous pressure with an increased outflow of fluid during the venous pressure rise (see fig. 8).

To compare with record III we show figure 6. This curve reproduces almost exactly their arterial curve. As can be seen, their increased outflow of fluid came while the arterial pressure was rising, dropped ap-

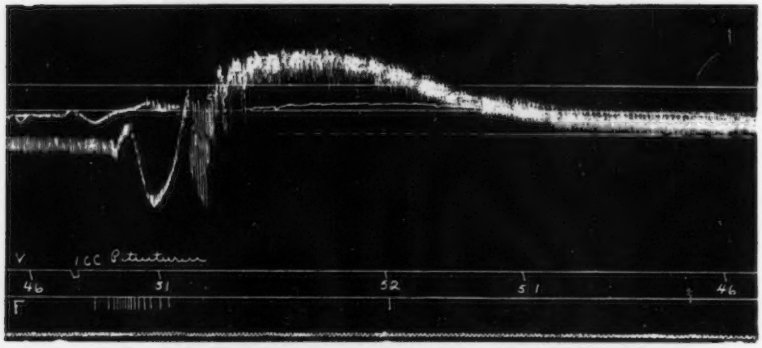


Fig. 8. This figure shows that with the preliminary fall in arterial pressure common soon after pituitrin injections there is frequently seen a marked rise in venous pressure; with this rise in venous pressure comes an increased outflow of fluid.

proximately to the normal rate when the highest point in the curve was reached, and practically ceased at a time when the arterial pressure was still far above normal. Our curve shows that at the time when their maximum outflow came venous and fluid pressures were rising synchronously; the former rose from 276 mm. to 356 mm., a rise of 80 mm.; the latter rose from 257 mm. to 324 mm., a rise of 67 mm. It is therefore self-evident that the cause of the increased outflow was not necessarily an increase in the amount of fluid in the skull, due to a choroidorrhea, it may have been—probably was—simply the expulsion of fluid by the increased venous pressure produced by the action of the drug. The cessation of flow with arterial pressure still high shown in records III

and IV means simply that enough fluid had been expelled to accommodate the venous blood accumulated in the sinuses, and further expulsion ceased. The failure of recession of the fluid finds a number of explanations: no negative pressure can be developed because of a lack of positive pressure in expelling the fluid, the high venous pressure may cause increased transudation, or what seems more plausible, the deficit in the vicinity of the needle is made good by fluid under positive pressure in other regions of the canal temporarily shut off from the needle by the position of the central nervous system. In actual fact we have seen the fluid recede in the cannula in several experiments, a fact which may

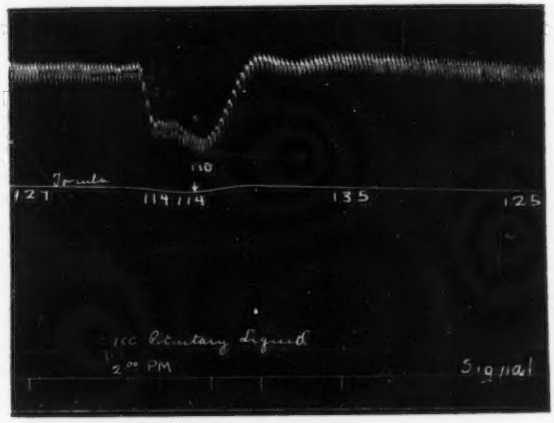
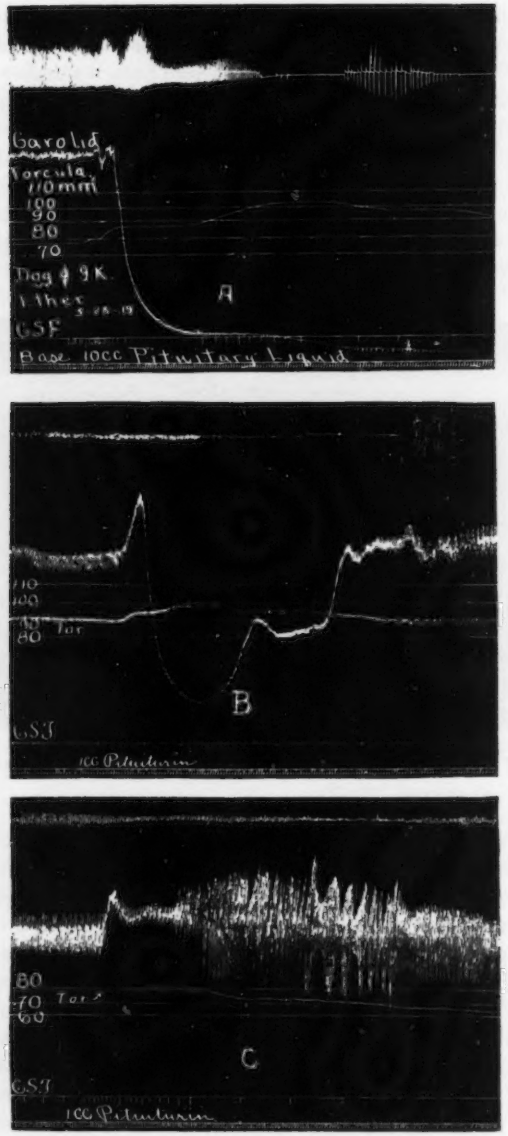


Fig. 9. This figure shows that after pituitrin the venous pressure may fall with the fall in arterial pressure.

point to the latter as the more likely of the three explanations offered. The differences in results in their tracings V and VI are due to differences in the behavior of the venous pressure in the two injections. We believe record V showed no effect on fluid outflow because there was no rise in venous pressure. We believe record VI shows the marked increase in fluid outflow because of a marked rise in venous pressure after the injection. As we pointed out before, the arterial pressure is no criterion of what is taking place in venous pressure, and while we have no basis for the assumption that venous pressure rose in record VI and did not rise in record V, we believe such is the case from our experience in similar conditions of experimentation. Weed and Cushing cannot


Carotid
Torcula
110mm
100
90
80
70
Dog # 9K.
Ether
CSF
A
Base. 10cc Pituitary Liquid
110
100
80 Tor
B
CSJ
10cc Pituitrin
80
70 Tor
60
C
CSJ
10cc Pituitrin

tell what happened in the vein during their experiments for the reason that they did not measure that pressure. To prove our point we cite tracings 8 and 9 where a fall in arterial pressure after pituitrin was in one case accompanied by a rise, in another case by a fall in venous pressure.

To compare with their record VII we show figure 10 *A*, an experiment in which following a large dose of pituitrin there was a marked fall in arterial pressure with increased fluid outflow. The remarkable fact brought out in our tracing is the fact that not only did the venous pressure rise from the first, but that it rose in two stages and each stage of increasing venous pressure was accompanied by an increased outflow of fluid, an increased outflow which was followed by a cessation each time venous pressure became stationary. It is therefore obvious that the factor which determines fluid outflow is not the actual venous pressure level, but the question as to whether the pressure is rising and the blood is accumulating in the sinuses. The venous pressure following pituitrin injections is not determined by the arterial pressure in the carotid, hence the mere fact that arterial pressure fell does not prove that venous pressure fell with it and hence the increased secretion of fluid is not the only cause of increased outflow. This increased outflow of fluid is just as satisfactorily explained by an increase in venous pressure or increased accumulation of venous blood as by increased secretory activity of the choroid. In fact there is no reason for invoking the latter at all, for all the facts are adequately explained by the former. Figure 10 *B* shows that pituitrin sometimes decreases fluid outflow, although venous pressure was rising slightly. Figure 10 *C* shows the optimum condition for outflow, increased arterial and venous pressures.

If further evidence were needed to show the dependence of the fluid on the vascular changes produced by the injection of extracts of the hypophysis, a study of all the changes shown in figure 5 should be convincing. The averages show a decided rise in all the pressures following the injection, and while the general arterial pressure returns to a lower

Fig. 10. This figure shows the different reactions of different dogs to the intravenous injection of commercial extracts of the hypophysis. Note in *A* a rapid outflow of fluid with a falling arterial pressure, also that the increased outflow is synchronous with the rises in venous pressure which occurred in two distinct stages. Note in *B* a similar fall in arterial pressure with only a slight rise in venous and a marked decrease in the rate of outflow. Note in *C* a rise in both arterial and venous pressures with a marked increase in the rate of outflow of fluid. These tracings show the importance of the venous pressure in the determination of the mechanism of fluid outflow.

level than at the beginning, all the other pressures remained at a higher level. The increase in the circle of Willis pressure, following the injection of hypophysis extract, an effect already referred to, would undoubtedly be sufficient to account for the high venous and fluid pressures. The point of particular importance, however, is the average change in the fluid; this is practically parallel with the average of the venous changes and if there were a decided increase in the fluid as is claimed, this would not be the case for if there had been a marked increase in fluid, the rise in fluid pressure would have been greater than that of venous pressure. By the manometer method, therefore, there is absolutely no evidence for any increase in the fluid and we believe that if Weed and Cushing had considered all the physical factors concerned in the outflow of the fluid, it would have been unnecessary for them to postulate a "choroidorrhea" to account for the changes they observed.

The increased flow of fluid following the injection of extract of pituitary body is due to the increase in the vascular pressure in the skull. The assumption that there is an increase in the amount of fluid is not necessary to explain the facts.

Frazier and Peet (2) conclude that brain extract has a specific effect because the rate for a given period following injection is greater than normal—in other words, more fluid escapes in a given period following the injection of brain extract than would have escaped in the same time with a normal rate of flow. This increase, they say, is independent of the fall in arterial pressure. We do not doubt that they observed an increased outflow of fluid, we ourselves have noted the same increase under similar conditions but with us, as can be seen from the table, there is a decrease in venous and fluid pressures in every case, just as there was in the case of the other depressor extracts, and not an increase in venous pressure as we have already pointed out Frazier and Peet believe to have occurred at the time the arterial minimum occurred. We are convinced that the increased fluid flow was due to the escape of preformed fluid lying in the adjacent cavities of the subdural space, an escape made possible by the marked shrinkage of the intracranial structures produced by the reduced arterial and venous pressures which permitted the fluid to escape past the natural obstructions and thus to appear at the most dependent portion of the canal, the *cisterna magna*, and escape through the needle. With the rise in arterial and venous pressures the intracranial structures again expand and the passage way is again obstructed, and a cessation of flow follows. Why nervous tis-

sue produces so much more marked an increase is obviously due to the more marked fall in arterial and venous pressures, and therefore to the greater shrinkage of structures and the freer transit of fluid through the straits. The above explanation makes it obvious that falls in arterial and venous pressures will not always produce an increased flow. With the dog on his side, the results are positive only in those cases where there is an accumulation of fluid over the cerebral hemisphere, the flow of which into the medullary region is impeded by the cerebral peduncle and the subcerebral vessels and sinuses. Thus many experiments are negative especially with the dog on his side.

Depressor extracts supposed to have a specific effect on formation of cerebrospinal fluid

The depressor effect of extract of nervous tissue is as marked as that of any other extract (1); in addition it is said to have a specific action on the increase of fluid (2) independently of the blood pressure changes. Dixon and Halliburton (4, p. 225) state: "This"—the brain tissue—"is the only tissue extract so far examined with the exception of choroid which gave a positive result on the cerebrospinal outflow." Frazier and Peet (2, p. 478) state: "The experiments with brain extract demonstrate that there is an actual increase in rate of flow of cerebrospinal fluid independent of the amount of fall of blood pressure."

A priori it is difficult to see in what respect extract of nervous tissue should so differ from other tissues as to produce a stimulation of the cells forming the fluid, for it is clear that the authors referred to above believe that brain extract stimulates fluid formation.

In order to satisfy ourselves regarding the effects of nervous tissue, fifteen injections of extracts of nervous tissue were made, including cerebrum, cerebellum, medulla, cord and pineal body. The changes produced were very similar for each of the extracts, and therefore only the effects produced by the cerebellum, which was typical for all, will be discussed in detail.

Six injections of cerebellar extracts were made into five dogs. In experiment 1 the injection produced a depressor effect on the arterial system, but the falls in venous and fluid pressures were slight. The final readings in all the pressures were lower than the initial ones. In experiments 2 and 5 injections of 5 cc. were made. In both cases there was a fall in arterial pressure with a comparable fall in venous and fluid pressures. Immediately following these injections there was an in-

TABLE 5

Extracts of cerebrum, cerebellum, medulla, cord, pineal, cerebrospinal fluid and aqueous humor

EXPERIMENT	ARTERIAL			CIRCLE OF WILLIS			TORCULAR VENOUS			CEREBROSPINAL FLUID		
	B	D	A	B	D	A	B	D	A	B	D	A
Cerebrum extract												
1	199	82	106				71	43	67	113	91	122
2	82	48	90	73	46	80	82	70	90	111	94	108
3	146	132	148	134	130	132	61	61	61	56	58	58
4	148	130	146	132	124	130	60	58	59	59	62	63
5	116	90	146	98	72	118	62	55	55	72	66	54
Average	138.2	96.4	127.2	109.2	93	115.0	67.2	57.4	66.4	82.2	74.2	81
Cerebellum extract												
1	106	72	88				67	61	55	121	100	102
2	120	76	110	88	48	80	71	57	79	64	40	65
3	110	70	96	76	44	68	67	58	76	58	35	53
4	90	48	88	80	48	68	90	66	83	108	99	100
5	148	120	148	136	120	134	51	49	61	51	50	57
6	86	48	114	74	40	96	85	68	110	85	58	92
Average	110	72.3	107.3	90.8	60.0	89.2	71.9	59.8	77.3	81.1	63.6	78.1
Medulla extract												
1	88	50	86	73	52	62	93	92	90	116	108	121
2	160	108	144	140	104	130	62	48	57	53	50	61
Average	124	79	115	106.5	78	96	77.5	70	73.5	84.5	79	91
Cord extract												
1	124	88	122	96	66	92	105	84	111	267	205	296
2	160	144	160	140	128	140	66	66	63	51	56	53
Average	142	116	141	118	97	116	85.5	75	87	159	130.5	174.5
Pineal extract												
1	118	98	86	100	86	74	90	87	85	63	67	71
2	128	74	138	106	60	116	115	85	85	102	79	76
Average	123	86	112	103	73	95	102.5	86	85	82.5	73	73.5

TABLE 5—*Concluded*

EXPERIMENT	ARTERIAL			CIRCLE OF WILLIS			TORCULAR VENOUS			CEREBROSPINAL FLUID		
	B	D	A	B	D	A	B	D	A	B	D	A
Cerebrospinal fluid												
1	124	124	120	96	96	96	75	79	75	82	82	78
2	154	154	146	114	106	106	322	330	368	187	190	205
3	156	154	156	116	115	113	319	322	321	299	302	301
Average	144.6	144	141.3	108.6	105.6	105	238.6	243.6	254.6	189.3	191.3	194.6
Aqueous humor												
1	148	152	136				124	118	93	131	130	107
2	156	154	152	111	108	105	316	317	308	300	301	296
3	124	120	122	98	94	94	91	94	95	148	154	152
Average	142.6	142	136.6	104.5	101	99.5	177	176.3	165.3	193	195	185

itial temporary rise in venous and fluid pressures of 3 mm. without any apparent rise in arterial pressure. Here the final arterial pressure was the same or less while the final venous and fluid pressures were greater than the initial pressures. This rise in fluid pressure cannot be interpreted as secretion because venous pressure rose also. In experiment 4 there was an initial temporary rise followed by fall in all the pressures. The general arterial pressure returned to normal but all the others remained slightly below normal. In experiment 6 there was a decided fall in all the pressure tubes; the final readings in each case were higher than the initial ones.

A study of the table will bear out the statement already made that the changes produced by cerebellar extracts are repeated with but slight variation by all the extracts of nervous tissue. It will further show a very marked similarity between the changes produced by extracts of nervous tissue and those produced by the depressor group previously discussed. The close correspondence of venous and cerebrospinal fluid pressures was very evident throughout. These pressures usually changed in the same direction as did the arterial pressure, but where the venous pressure did not follow the arterial neither did the fluid pressure follow it. In fact in every case the venous and fluid pressures ran almost exactly parallel. Allowing for error in the method, there was no evidence whatever of any increase in fluid that might be interpreted as secretion.

Whatever the significance of the initial temporary rise preceding the pressor effect may be, it certainly gives additional emphasis to close relationship between fluid and vascular changes. Though the rise in arterial pressure is slight and of short duration, it is sufficient to produce corresponding changes in the fluid by means of the venous change; that it is the venous pressure that here affects the fluid pressure is shown by the fact that the changes take place almost simultaneously in venous and fluid pressures and a little later than the alterations in the

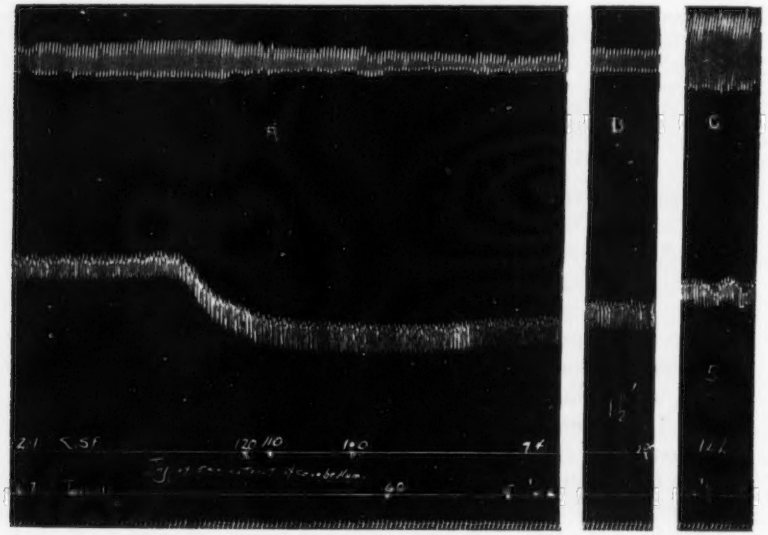


Fig. 11. This figure shows the effect of the injection of 5 cc. of cerebellar extract. *B* is taken 1½ minutes after the end of *A* and *C* 5 minutes after *A*.

arterial pressure. It has already been shown that a rise in fluid pressure does not produce a rise in venous.

The average of all the changes in each of the pressure tubes is as convincing here as with kidney extract, in showing that the fluid reflects vascular changes. The averages show a distinct fall in each of the pressures followed by an average return to normal with the exception that venous pressure was less than the average for the initial reading.

We are sure that they observed an actual increase in the outflow of the fluid under influence of nervous tissue extracts, but we cannot con-

cur in their conclusions. In the first place they have based their conclusion for a mechanical outflow on the observation, which our work would show to be incorrect; namely, that there is a rise in venous pressure corresponding with the fall in arterial. A study of their tracings, figures 9 and 10, shows unmistakably that the increased outflow accompanies the vascular change. Had they measured venous pressure simultaneously with arterial in their actual experiments they would undoubtedly have observed a corresponding fall in the venous pressure, a fall which would have made increased outflow possible as described earlier in the paper. In figure 11 we show a typical graph.

Dixon and Halliburton (4) likewise claim a specific action for brain extract but their evidence is less convincing than that of Frazier and Peet. They do not even show the arterial pressure on their tracing (fig. 4), hence one cannot even guess what factors may have been concerned in producing the slight outflow they record.

Extracts of choroid plexus

The extract from the choroid plexus is another depressor extract for which a specific action is claimed, in causing an actual increase in the fluid. In order to determine the effects of this extract by the manometer method, twelve injections were made into eight different dogs. The extracts were all made from fresh dog choroids, with the exception of one, which was made from fresh sheep choroids. Following seven of these injections, there was but a slight vascular change; the remaining five gave a quite marked depressor effect.

In experiment 1 the extract from one choroid was injected. There was no appreciable change in arterial pressure but there was a rise in venous and fluid pressures. In experiment 2 the injection of 10 cc. choroid extract produced practically no effect on arterial pressure, but venous and fluid pressures rose slightly. The final readings of the latter were higher than the initial readings. The second injection in experiment 8 gave a slight fall in arterial pressure accompanied by a transitory rise in venous and fluid pressures. This is the only well-marked example of a result such as Dixon and Halliburton call the usual one. (See fig. 12). The usual result is one with all pressures falling as is usual with tissue extracts. (See fig. 13). These pressures fell slightly but again the final readings were higher than the initial ones. Neither of the injections in experiment 5 produced any appreciable effects on arterial pressure—the changes in venous and fluid pressures were slight

but entirely comparable. The injection in experiment 3 (2 cc.) gave little arterial change with slight changes in venous and fluid pressures; again the latter were quite comparable. The injection ($2\frac{1}{2}$ cc.) in experiment 10 produced quite a marked depressor effect on the arterial side with a corresponding fall in venous and fluid pressures. All of the final readings were lower than the initial ones. The injection (2 cc.) in experiment 7 gave little arterial change with slight changes in venous

Fig. 12. This figure shows the result of an injection of choroid extract in which there was a marked fall in arterial pressure accompanied by an appreciable rise in venous and fluid pressures. Note that the maximum in each of these two pressures occurred after the maximum fall in arterial pressure. Later all the pressures rose to above normal, the change in venous pressure being adequate to explain the change in fluid pressure.

and fluid pressures, the latter being quite comparable. The first injection (2 cc.) in experiment 9 gave a decided fall in arterial pressure, accompanied by a fall in venous and fluid pressures. Here again all the final readings were less than the initial ones. A second injection (exper. 4) produced quite similar changes, except that they were less marked; in this case the final readings of the venous and fluid were higher than the initial ones. The injection in experiment 8 produced a very marked fall in arterial pressure. Almost simultaneously with the

low point in arterial pressure, the high point in venous and fluid pressures was reached; then with the rise in arterial pressure there was a fall in venous and fluid pressures, but they remained higher than they were before injection. (See fig. 12). This is the *one* experiment in our series which produced a well-developed effect, a change such as Frazier and Peet describe and which they claim is typical. The injection of 2 cc. sheep's choroid in experiment 11 gave a fair depressor effect on arterial pressure with an accompanying decline in venous and fluid pressures; the changes in the latter were entirely comparable. The injection of sheep choroid extract in experiment 12 produced a decided

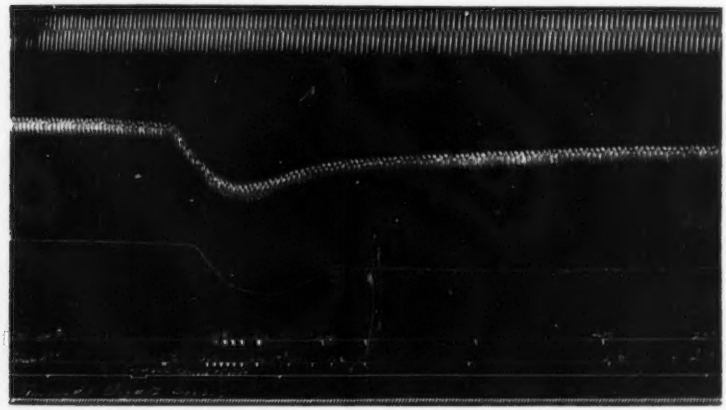


Fig. 13. This figure shows the result of the injection of 2 cc. of choroid which was followed by a fall in all the pressures under observation. Later all the pressures returned almost but not quite to the normal. Contrast this with figure 12.

fall in arterial pressure together with entirely comparable changes in venous and fluid pressures.

Reviewing the action of the injections of choroid plexus it will be noted that in those cases where there was little or no vascular change, there was likewise little change in the fluid. Where there was a change in fluid, there was almost invariably a corresponding change in venous pressure even though no change in arterial pressures was noted. The injection in experiments 9 and 12 shows a typical change following any depressor substance, i.e., a decided fall in arterial pressure accompanied by a corresponding fall in venous and fluid pressures. The changes

produced by the injection in experiment 8 were exceptional; however, the fact that such changes as these do occur occasionally (a few typical cases in 90 injections) shows unmistakably the importance of taking venous pressure simultaneously with arterial and fluid pressures, if one wishes to draw conclusions from the effect produced by vascular changes. Accompanying the low point in arterial pressure was a decided increase in respiration; this with the high venous pressure would give rise to a condition which would favor a marked outflow of the fluid with the cannula method. Again this experiment would show the error of Dixon and Halliburton's conclusion. By taking the venous pressure in

TABLE 6

Extract of choroid plexus

EXPERIMENT	ARTERIAL			CIRCLE OF WILLIS			TORCULAR VENOUS			CEREBROSPINAL FLUID		
	B	D	A	B	D	A	B	D	A	B	D	A
						Choroid plexus						
1	153	154	154	118	118	117	138	140	145	143	150	158
2	120	116	120	96	96	94	75	83	78	77	81	78
3	124	118	128	94	88	96	78	84	84	79	83	86
4	128	116	136	80	67	79	246	224	261	228	211	244
5	114	110	110	94	92	94	81	77	92	95	96	105
6	110	112	108	88	88	84	95	98	88	107	109	100
7	90	88	88	64	66	62	260	264	233	128	133	131
8	138	90	140				85	134	106	96	142	102
9	146	106	126	90	59	75	272	198	245	242	194	238
10	112	86	94	94	68	80	281	189	204	107	89	91
11	112	86	118	100	78	106	102	69	83	77	68	74
12	132	66	122	118	54	98	105	58	115	125	88	106
Average	123.2	104	120.3	94.1	79.4	89.5	151.5	134.8	144.5	125.3	120.3	126.0

one animal and the fluid pressure in another, they concluded from their results that venous and fluid pressures did not run parallel. Because they observed the rise in the fluid earlier in one experiment than in the venous pressure in another, they decided that the fluid had an independent secretory pressure. The error in their method of observation has already been pointed out (6), and not only this one but practically all our experiments show conclusively that venous and fluid pressures run, within the limits of experimental error, parallel. Also we have in experiments 1, 2 and 3, table 6, instances in which there was no change in arterial but where there was rise in fluid, with a parallel rise in venous pressure.

Dixon and Halliburton concluded from an increased rate of outflow of fluid from a cannula, that there is an actual increase in the amount of fluid. They discuss the possibility of physical factors which might influence the outflow, but they do not eliminate these possibilities by actual experiment. For example, they eliminate the argument that a fall in arterial pressure might cause a rise in venous pressure in the following way: "(1) increase in venous volume will be counteracted and probably counterbalanced by decreased arterial volume, so that the change of brain volume will be negligible; (2) the fall of blood pressure is not always seen; and (3) other substances which cause a depressor effect do not increase the cerebrospinal flow." Over against their argument (1) we would place our result obtained in experiment 8 showing that a rise in venous pressure does follow a fall in arterial pressure in some cases. (2) We also admit that a fall in blood pressure is not always seen, still we would refer the reader to experiments 1, 2, 3 and 5 with choroid injection in which there was a rise in venous pressure with no change in arterial. (3) In none of our whole series of experiments with depressor extracts did we observe any indisputable evidence of increased formation of fluid, hence it would appear that if Dixon and Halliburton had eliminated all the physical factors, they would not have observed the increased flow with choroid extract without some vascular change to explain the outflow. The effect of respiration observed by them is directly opposite to that reported by us in many cases in an earlier paper, and if as they say choroid extract accelerates respiration then one should expect in many cases an increased outflow rather than a decreased. The lack of response of a second injection would depend, as has been shown, on the amount of fluid in the canal rather than on the lessened effect of the chemical substance or hormone "which stimulates the secreting epithelium of the choroid gland to become active." If the mechanical factors could account for all the outflow, then it would not be necessary to assume that atropine—a substance which inhibits the activity of organs known to have secretory activity—does not effect the choroid gland, for Dixon and Halliburton state that "the increased flow is seen equally well after the injection of atropine." This action of atropine, in the light of our own experiments, would simply be an additional argument in favor of a mechanical cause for the outflow.

There is one more fact in connection with the action of the extract of the choroid which should be mentioned. If the extract of the choroid does have an action upon the choroid plexus, the point of action is not confined to that structure. Figure 14 shows the result upon the lymph

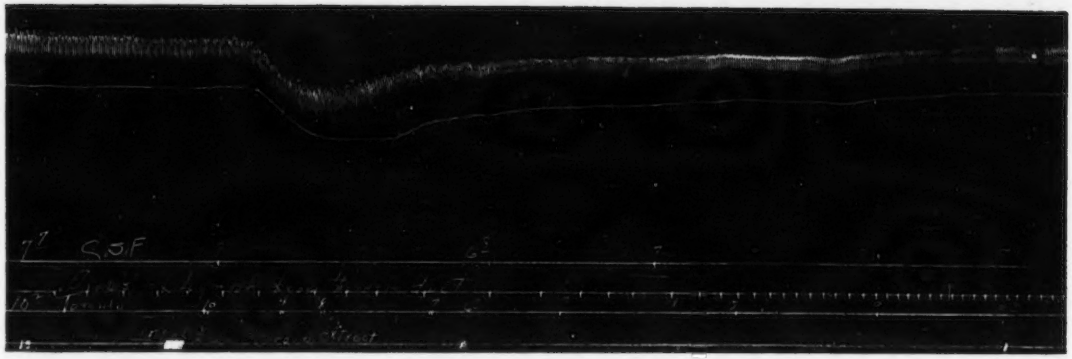


Fig. 14. This figure shows that choroid extract acts at points other than the choroid plexus. A definite lymphagogue action is shown by the increased outflow of lymph from the thoracic duct.

flow from the thoracic duct of the injection of 2 cc. of sheep's choroid into a dog. This has been confirmed by three other experiments. In two of these cases the extract was fully as active as a 2 per cent solution of peptone.

Thyroid extracts

Thyroid extract is another of the depressor extracts which is said to have a specific action, but instead of stimulating the choroid plexus to excreased activity, it is said to inhibit the flow of cerebrospinal fluid. In order to determine whether the action of thyroid was really specific as claimed, a series of nineteen injections was made into thirteen different dogs. The extracts used was made from normal and enlarged dog thyroids, from the commercial preparation and from pathological human thyroids.

Five cubic centimeters of extract from a *normal* thyroid were injected in experiment 8. A pronounced fall in arterial pressure resulted, accompanied by an initial transitory rise and then a fall in venous and fluid pressures, entirely comparable with the fall in arterial pressure. The final arterial pressure was lower but the venous and fluid pressures were both higher than the initial reading. In five other injections, including extracts from normal and abnormal thyroids, in which a distinct fall in arterial pressure was observed, the changes in the fluid were, with slight variations, the same as in experiment 8. A fall in arterial pressure was accompanied by a fall in venous and fluid pressures. The final fluid pressure always depended on the venous pressure.

The injections which had a slight or negligible action on the arterial pressure gave relatively less change in the venous and fluid pressures. In a small number of these, the fluid and venous pressures rose very slightly while the arterial pressure fell, showing again the close correspondence between venous and cerebrospinal fluid pressures.

The results observed following the injection of extracts of desiccated thyroid were quite similar to those already described. The fall in arterial pressure was accompanied by a fall in both venous and fluid pressures, and at the final reading the venous and fluid pressures stood higher than before injection.

The injection of 7 cc. of extract from a pathological human thyroid in experiment 18 gave a decided fall in arterial pressure with a comparatively small drop in venous and fluid pressure. The venous and fluid pressures rose with the arterial pressure so that the final pressures were practically identical with the initial ones. The injection of 10 cc.

pathological thyroid extract in experiment 19 gave but a slight fall in arterial pressure with a comparatively small change in venous and fluid pressures.

It will be observed from the record of the changes produced by thyroid extract that the changes are in no way different than those produced by any other one of the depressor extracts. The changes in venous and fluid pressures are entirely comparable. If additional evidence

TABLE 7

Extract of thyroid

EXPERIMENT	GENERAL BLOOD PRESSURE			CIRCLE OF WILLIS PRESSURE			VENOUS (TORCULA) PRESSURE			C. S. F. PRESSURE		
	B	D	A	B	D	A	B	D	A	B	D	A
Thyroid extracts												
1	116	90	122	82	57	84	90	88	86	70	58	48
2	124	70	108	80	52	64	98	80	100	97	60	60
3	130	104	124	104	90	100	63	56	57	65	63	58
4	120	108	122	98	84	98	53	50	50	53	50	48
5	152	148	160				59	62	81	48	55	71
6	162	144	158				88	96	108	79	94	108
7	130	92	124	119	84	112	120	81	122	154	134	167
8	154	90	130	116	94	116	94	70	99	87	80	95
9	126	114	114	118	114	110	101	100	98	95	100	101
10	114	68	90	90	56	66	92	69	80	292	162	190
11	102	92	104	80	79	80	76	76	77	275	280	288
12	152	124	132	102	77	83	296	255	262	287	240	260
13	118	94	116	92	78	92	100	101	105	134	130	145
14	92	82	84	70	68	64	248	236	229	94	93	106
15	124	114	114	106	96	98	78	77	86	73	65	63
16	132	132	132	110	106	106	80	80	76	72	74	76
17	120	114	118	94	92	92	97	98	98	148	147	138
18	168	100	164				56	34	56	44	27	42
19	84	72	66				14	00	−10	7	−10	−30
Average	127.3	102.7	120.1	97.4	81.8	91.0	100.1	89.9	97.9	114.4	100.1	107.9

were desired, a study of the figure 5 showing the averages for all of the pressures should be convincing. The average change for nineteen injections shows conclusively the dependence of the fluid pressure on the vascular changes for not only is there a close correspondence between fluid and venous changes, but between the fluid and arterial as well. There is absolutely no evidence for a decrease in the amount of fluid as determined by the manometer method. Frazier and Peet's observa-

tions are that "thyroid extracts give a decrease in the rate of fluid outflow," but the evidence that they present is not conclusive. It is true that in our work individual experiments could be cited in which there is an apparent decrease in the fluid, but other experiments could be cited in which there is an apparent increase in the fluid. An average of all the changes eliminates these exceptional cases and therefore we believe that the average rather than the individual change comes nearer showing the true condition.

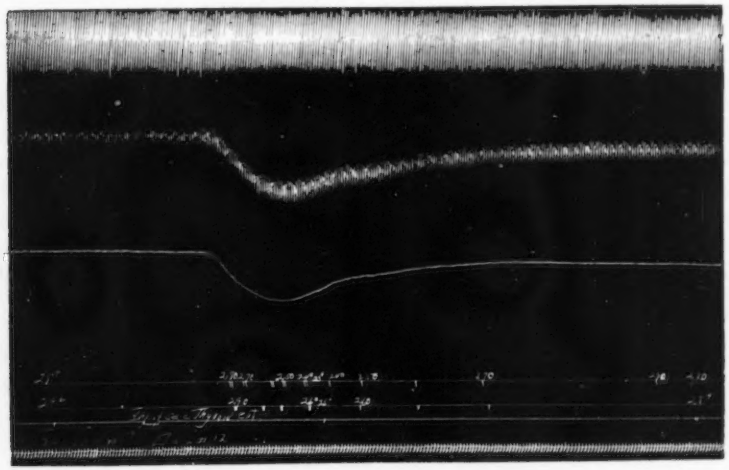


Fig. 15. This figure shows the effect on all the pressures of the injection of 5 cc. of thyroid extract. Note the fact that all pressures fell, only to return almost exactly to the normal.

Frazier and Peet (19) further state that "the decrease in rate appeared almost immediately after the injection and lasted for four and one-half hours" and that "control experiments have demonstrated that with the method we used the fluid will flow at a nearly uniform rate for this length of time." Since this method has already been fully considered, it is unnecessary to re-open the discussion here; however we must say that in the experiments with this method, our findings were similar to those of Dixon and Halliburton on this point, who report a marked slowing in the rate in the normal animals run as controls; a slowing which compares exactly with the slowing recorded by Frazier and Peet but which according to them is due to the thyroid injections.

A reference to the table shown by Frazier and Peet on the normal rate of flow (p. 275) does not bear out their statements regarding the results on their controls. They cite two animals—the first ran seven and one-sixth minutes with a marked tendency to decrease, as can be seen in their protocol at a glance; the second showed a very marked irregularity of rate and has the following note added—"stopped flowing, dog killed with chloroform." This experiment ended in eighteen minutes.

We do not doubt the observations recorded by the authors but we do not believe that in a series of ten dogs, more than one in that number would give a marked flow after three or four hours under anesthesia. This is in accord with Dixon and Halliburton who, using practically the same method, find no flow after the fifth hour.

A careful consideration of all the evidence seems to present no good reason for believing that thyroid extract causes a decrease in the amount of fluid. In the first place, control experiments show a decrease in outflow, which is in every respect comparable to the decrease in the fluid claimed by Frazier and Peet following thyroid injections. Furthermore, when the manometer method is employed, the changes following the injection of thyroid extract are no different than those produced by any one of the depressor extracts used.

It would appear, therefore, that the changes in the fluid following the thyroid injection are to be explained entirely by vascular changes and that the claim that thyroid has a specific action is not based on a true interpretation of facts.

CONCLUSIONS

1. Nearly all tissue extracts have a depressor effect on the vascular system; extracts of adrenal and of the posterior lobe of the hypophysis have a pressor effect.

2. Changes in arterial pressure were usually accompanied by corresponding changes in torcular (venous) pressure; there were occasionally, however, important exceptions in which changes in arterial and torcular pressures were exactly opposite.

3. The changes in fluid pressure corresponded quite closely to the venous changes. While the arterial pressure may have a direct effect on the fluid pressure, the changes in the fluid were for the most part due to the venous changes.

4. The changes in the fluid were quite comparable with all the tissue extracts having a depressor effect, likewise with those having a pressor

effect. In every case the fluid changes depended on the vascular changes, not upon new formation.

5. There is no indisputable evidence that any of the extracts used have a specific action on the fluid.

6. The changes produced in the fluid by tissue extracts are mechanical in so far as these extracts have any vascular effect.

7. Extracts of the choroid plexus have a definite lymphagogue action.

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PROCEEDINGS OF THE AMERICAN PHYSIOLOGICAL SOCIETY

Thirty-Second Annual Meeting

Cincinnati, December 29, 30, 31, 1919

The time relations of the heart cycle as shown by the carotid pulse of man. Warren P. Lombard and Otis M. Cope.

The paper treated of work which was a continuation of that reported at the last two meetings of the Society. The duration of the systole of the left ventricle should give evidence of the functional condition of the muscle of the human heart. The carotid pulse tracing was used by the writers to obtain evidence of the length of the systole, because it would be of general, practical application in case the method proved of value. The time between the beginning of the rise of the primary wave and the beginning of the rise of the dicrotic wave, the P-D time, does not include the period of rising tension in the ventricle, and would, therefore, be perhaps 0.030 second shorter than the true systole of the ventricle. Nevertheless, it should give a good indication of the action of the heart muscle.

The pulse rate and the position of the subject have an important effect on the duration of the systole, and to establish a standard which should be a gauge of the condition of the heart muscle it was necessary to establish the P-D interval and the D-P interval (the time between the beginning of the rise of the dicrotic and the beginning of the rise of the primary wave), for every ordinary pulse rate when the subject was standing, sitting and lying down. This was done and, in addition, the P-D and D-P intervals were determined for subjects standing, immediately after light exercise.

A table summarizing the results, for cycle lengths from 1.200 to 0.300 seconds (pulse rates 50 to 200) was shown. Curves picturing the rate of the shortening of the P-D time, when it was plotted with cycle lengths, and plotted with pulse rates, as abscissae, and also formulae which permit the calculation of the normal, average P-D interval by men standing, sitting, lying down and standing just after exercise, were exhibited. The formulae were different from those offered at the last meeting. These results were based on 620 tests on 250 normal men, the length of the P-D and D-P intervals having been measured to thousandths of a second in more than 10,000 cycles.

It was stated that the P-D and D-P intervals are both altered by respiratory and vasomotor influences; that the P-D interval is affected more by respiratory, and the D-P interval often more by vasomotor influences; that the changes in the length of the P-D and D-P intervals

produced by the respiratory and vasomotor influences do not necessarily occur to like degrees or synchronously, and consequently are probably brought about in different ways. It was suggested that the P-D interval was influenced more through the amount of blood supplied to the left ventricle, and the D-P interval through the nerves controlling the heart rate.

The length of the P-D interval was not found to be appreciably affected by age, height or weight. The systolic, diastolic and pulse pressures, occurring within normal limits, were not found to alter the P-D interval. On the other hand, women were observed to have longer systoles, on the average, than men.

Further observations on the relation of the central nervous system to epinephrin secretion. G. N. STEWART and J. M. ROGOFF.

Our former experiments on the epinephrin output after transections of the spinal cord at different levels in cats have been confirmed and extended by a new series of experiments.

1. In eleven acute experiments the cervical cord was divided at levels from the fourth to the seventh segment. In several of the animals the initial output was undiminished by the section, in the others it was more or less diminished but a substantial output could still be estimated. In eight dogs (section at 4th to 6th segment) and two rhesus monkeys (6th to 7th segment) a considerable or marked diminution in output after the cord section was observed, apparently corresponding to the greater degree of shock than in cats, but even in the monkeys a substantial output could be estimated.

In three cats the brain and bulb were eliminated by ligating the arteries. It was shown by the usual tests that the anemia was complete. In all three experiments the epinephrin output was the same as before elimination of the brain and bulb, a full normal output.

2. In fifteen experiments on cats and dogs in which the animals were allowed to survive for two to thirteen days after cervical transection the output never attained the normal average and was usually much below it, although in several of the experiments the output attained a third or a half of the normal average.

3. Acute experiments with dorsal cord transections were made on a number of dogs and cats (4th to 5th segments) and one survival experiment (7 days) on a dog. The output was greatly diminished or abolished within the limits of detectability by the assay.

4. Strychnine caused a marked increase in the output both in acute and survival experiments after cervical cord transection.

5. The output of epinephrin in the above experiments was estimated by the methods previously employed by us, entailing opening of the abdomen, because we do not know of any other way at present by which quantitative estimations of the output can be made. To test the objection that opening the abdomen may profoundly alter the functioning of the adrenal secretory mechanism we have made experiments on cats with denervated heart in which the acceleration of the

heart produced by stimulation of the central end of the sciatic was compared before opening the abdomen with that obtained after it was opened and such manipulations made as would be involved in forming a cava pocket. We did not find that the reaction was essentially altered. Further experiments on cats with denervated heart confirm our previous conclusion that reactions obtained on the denervated limb and denervated heart (von Anrep, Cannon) do not constitute a demonstration of augmented epinephrin output with asphyxia and nerve stimulation until it is shown that redistribution of the blood with the ordinary output of epinephrin cannot account for the reaction.

The influence of oxygen deficiency and related conditions upon the hemato-respiratory functions. YANDELL HENDERSON and HOWARD W. HAGGARD.

It is generally supposed that under oxygen deficiency acids are produced in the tissues and are retained in the blood, and that the blood alkali is thus neutralized and eliminated through the urine. This may be termed the acidotic process.

Experiments on dogs subjected to progressively decreasing oxygen show, however, that the process actually involved is in many respects exactly the opposite of the usual supposition. They demonstrate that before any considerable amount of alkali is lost an abnormally large amount of CO_2 is eliminated by the excessive breathing induced by a lowered oxygen pressure in the air breathed. Then alkali passes out of the blood to compensate this alkalosis. This we term the acapnial process.

From these facts and related observations on men it appears that in normal persons the blood alkali is controlled by the dissolved CO_2—more or less alkali being called into use in the blood to satisfy the normal H_2CO_3: $NaHCO_3$ relation, and thus to keep the CH of the blood nearly constant. The amount of dissolved CO_2 in the blood is controlled by the pulmonary ventilation, and fundamentally in normal persons the ventilation is adjusted to the oxygen partial pressure of the altitude at which the person lives.

When, however, over-breathing is induced and the H_2CO_3 of the blood is reduced, the $NaHCO_3$ follows downward. This, we find, and not acidosis, is what occurs also in carbon monoxide asphyxia.

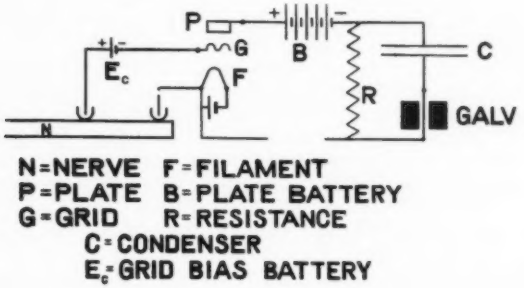
A simple test for differentiating between low blood alkali of acidotic and that of acapnial origin is the administration of air to which 8 to 10 per cent of CO_2 has been added. This quickly causes death in acidotic subjects; but it induces a rapid recall of alkali to the blood, and restoration of the subject to a virtually normal condition of health if the condition is of acapnial origin.

We have now (in collaboration with Dr. R. C. Coburn) applied this treatment to patients after surgical operation and anesthesia. The result has been that alkali was recalled to the blood, that arterial pressure and other functions were restored to normal, and that the anesthetic was rapidly eliminated by the full breathing during the CO_2 inhalation with a consequent great reduction of nausea.

In dogs asphyxiated with carbon monoxide (in investigations for the U. S. Bureau of Mines) strikingly beneficial results have been obtained by means of oxygen reënforced with 10 per cent CO_2.

Electron tube amplification with the string galvanometer. ALEXANDER FORBES and CATHARINE THACHER.

Acting on a suggestion of Dr. H. B. Williams we have developed a method of using an electron tube to amplify those action currents in the nervous system, which are too small to record satisfactorily with the string galvanometer unaided. We used a "D-tube" loaned by the Western Electric Company. The device consists of a vacuum tube with a cathode in the form of a filament heated to incandescence by a current, an anode in the form of a metal plate and an auxiliary electrode in the form of a grid between the two. The hot cathode emits electrons, thus enabling a current to pass from plate to filament



within the tube if properly connected with a battery. If the grid is made positive with respect to the filament the plate-to-filament resistance is lowered; if negative, it is raised. Thus the current in the tube is regulated by variations in the potential of the grid. Small variations in grid potential can produce large variations in the plate current; thus the tube acts as a relay, reproducing greatly amplified, the impressed E. M. F.

The string galvanometer cannot be placed directly in series with the battery and the tube; the resulting current would destroy the string. At the suggestion of Mr. Sewall Cabot the string was protected by placing a large condenser in series with it, and the current was shunted by the string and condenser through a resistance and of the same order of magnitude as that of the tube. The arrangement is shown in the accompanying figure. The resistance and the tube being connected in series with a battery of fixed voltage, a change in tube resistance will cause a change in potential difference across the tube. This will cause current to flow from one plate to the other of the condenser through the string. By using a condenser of very large capacity a source of

current is obtained which is practically constant throughout the brief duration of an action current in nerve or muscle. In other words, the partial discharging of the condenser following a disturbance of equilibrium is so slow that no appreciable distortion results in the amplification of a brief action current. The battery E_c in the grid circuit is introduced to give a bias, or initial negative potential, to the grid. This serves to make the device function as an electrometer in that the excursions of the string are independent of the resistance in the tissue. It increases the amplification.

The amplificaton obtained with this device depends on the resistance of the tissue in circuit between the electrodes, and in part also on the resistance of the string. If the resistances of both tissue and string are very small there will be no amplification; if the resistance of either is large there will be. With a tissue resistance of 50,000 ohms about 25-fold amplification may be obtained.

A wiring scheme has been installed whereby it is possible to shift from the standard arrangement of the galvanometer to the electron tube arrangement in about two minutes, by merely throwing a few switches and making two or three minor adjustments.

The following values of the various qualities involved have been found with a "D-tube" efficient and convenient; filament current, 1.10 ampere; grid potential, −1.5 volt (one dry cell); plate battery voltage, 275; resistance, 50,000 ohms; condenser, 15 microfarads, (made up of Western Electric paper condensers).

The complete account of the work will appear soon in this Journal.

Observations on the pathological physiology of chronic pulmonary emphysema. R. W. Scott.

Two individuals with well-marked chronic pulmonary emphysema of the so-called "large lung" type have been studied over a period of several months. It was found that these patients breathe high percentages of CO_2 (8 to 11 per cent) for a period of ten to fifteen minutes without any marked distress and with little increase in the minute volume over that observed while breathing room air. As an explanation of this unusual tolerance to inspired CO_2, two possibilities were considered; *a*, some interference with the passage of CO_2 from the lung air into the blood; *b*, an increased capacity for the storage of CO_2 in the blood and body fluids.

To study the question of pulmonary permeability, experiments were done to ascertain the rapidity with which equilibrium was established between the CO_2 of the blood and the lung air. A procedure similar to that described by Henderson and Prince was employed after four or five rebreathings, the CO_2 of the lung air reached a constant level which was definitely higher than that found under similar experimental conditions in normal individuals. Equilibrium was reached at the same high level and in approximately the same length of time when the air first inspired contained either a low (room air) or a high percentage of CO_2 (12 to 14 per cent). A level of about 9.4 per cent of

CO_2 was reached in the subjects with emphysema as compared to 7.2 to 7.4 per cent CO_2 in the cases of several normal individuals observed. Confirmatory evidence for these results was afforded by the direct determination of the total CO_2 content of the arterial and venous plasma together with estimations of the H-ion concentration of the whole blood (arterial) as drawn. In the case of emphysema the arterial CO_2 averaged 75 vols. per cent (0°–760 mm. Hg.) and the venous CO_2 80 vols. per cent. In a series of 19 normal individuals the arterial CO_2 averaged 57 vols. per cent and the venous CO_2 63 vols. per cent. The pH of the whole blood (arterial) in the case of emphysema was normal. These facts indicate that both the free and combined CO_2 of the blood are elevated but the ratio $\frac{H_2CO_3}{NaHCO_3}$ and hence the CH is maintained normal. Apparently the degenerative process in the lung leads ultimately to diminished aeration of the blood. The free CO_2 is elevated, and as a compensatory measure to keep the CH within narrow physiological limits, the bicarbonate is maintained at a high level which appears to be permanent. This condition in man is analogous to that found in animals made to breathe air rich in CO_2. Both cases clearly demonstrate that the bicarbonate content of the blood and body fluids is not a fixed quantity, but may undergo a considerable increase to combat an impending CO_2 acidosis. Since the buffer value of blood is directly proportional to the bicarbonate content, it seems probable that in the case of emphysema a higher percentage of CO_2 in inspired air is required to produce a given elevation in the blood CH. However, when this level is reached the ability to prevent a further increase is limited because of the definite impairment in lung ventilation in chronic emphysema.

Observations on the physical efficiency tests used by the Royal Air Force of England. EDWARD C. SCHNEIDER.

In England under the guidance of Lieutenant-Colonel Martin Flack a set of simple physiological tests was devised to indicate subjects who were likely to suffer from discomforts in the air, symptoms which might be due to lack of proper oxygenation of the blood and were likely to render the man unfit for flying. The tests grew in number with experience and the application was extended to detect flying stress or fatigue.

An analysis of the records of American aviators who underwent the rebreathing examination and the English set led to the conclusion that these tests do not give a reliable indication of how well a man will respond to diminished oxygen tensions. The data are not capable of physiological interpretation unless they represent the best effort that can be put into each test. Indifferent subject and listless observer both vitiate the results. The tests are in some respects psychological, since if a man determines to hold the breath until discomfort is pronounced it can be done or he may give up with the first feeling of effort. To sustain the mercury column in the "fatigue" test requires as well

some skill, and a proper set of lips may ease the performance so much that 10 to 20 seconds are added to the length of the hold. The expiratory force test requires effort and experience. One often improves his record appreciably after several performances. The mental attitude of the subject may make or mar these tests. Therefore it is believed that the tests depend too much upon the hearty coöperation and the complete attention of the subject.

The influence of low oxygen tensions on venous blood pressure in man. EDWARD C. SCHNEIDER.

Low oxygen tension effects on the venous blood pressure were studied during a period of gradual decrease in which the lower limits of the partial pressure of oxygen ranged between 48 and 79 mm. Hg. The experiments lasted from 25 to 45 minutes. Three methods were employed to obtain low oxygen tensions, the low pressure chamber; rebreathing of air, from which the carbon-dioxide produced by the subject was removed by sodium hydroxide, at normal atmospheric pressure; and air diluted with nitrogen. All observations were made on officers and enlisted men at the Medical Research Laboratory of the Air Service, U. S. Army.

The effects on the venous pressure were the same regardless of the method used to vary the oxygen. This is interpreted as proof that the effects were not the result of a mechanical action but the result of the changes in oxygen.

The general response in the venous pressure during the reduction in oxygen was a fall that ranged between 22 and 146 per cent of the individual's sea-level normal. In 48 per cent of all cases the fall, which was gradual, began within the first five minutes, in which time the oxygen decreased from 21.96 to about 18.5 per cent, or from 159 to 140 mm. partial pressure. In 19.6 per cent of cases the drop first appeared between the fifth and tenth minutes or by the time the oxygen had decreased to 16 per cent (122 mm.). The rate of fall in the venous pressure was ordinarily most rapid after the oxygen reached 12 per cent (91 mm.). In 4 out of a total of 56 experiments this venous response failed to occur.

Circulatory reactions to hemorrhage. WALTER J. MEEK and J. A. E. EYSTER.

The reactions to hemorrhages amounting to as much as 2 per cent of the body weight have been studied in a series of anesthetized dogs by means of the X-ray, arterial and venous pressure manometers and the cardiometer. In the intact morphinized animal the diastolic size of the heart is maintained until about 2 per cent of the body weight of blood is lost. The hemoglobin determinations indicate no important restoration of blood volume during this period. Blood pressure and heart rate remain unchanged.

In the anesthetized animal with open chest and artificial respiration, the volume output per minute and the volume output per beat remain

unchanged until about 1 per cent of the body weight of blood is lost. There is then a rather abrupt decrease. Recovery after each bleeding becomes poor. Systolic and venous pressures also fail to recover their normal level and the pulse rate is permanently increased.

On the basis of these facts it may be concluded that after small hemorrhages there is some other mechanism than those usually recognized which insures a normal return of venous blood to the heart in spite of the reduced volume. A possible explanation might be found in a decreased capacity of the venous cisterns together with an increased velocity of the blood returning to the right heart. This, however, remains to be demonstrated.

Studies on the responses of the circulation to low oxygen tension. II. The electrocardiogram during extreme oxygen-want. CHAS. W. GREENE and N. C. GILBERT.

Tests were made of the low oxygen endurance of twenty-two men by the rebreather method. Clinical records were taken at minute intervals of the pulse rate, systolic and diastolic blood pressure, respiratory rate and minute-volume. Electrocardiograms were taken at periods of five minutes during the first two-thirds of the test and at two-minute intervals in the last third. Attempt was made to secure an electrocardiogram just before the close of the experiment and a check was taken just after closing the test. Of the twenty-two soldiers tested, eight or about 36 per cent showed irregularities of the heart rate and type of beat. The heart rate accelerates rapidly toward the close of the rebreather test, a fact well established by the published experience of the Medical Research Laboratory of the Air Service. The Air Service also reports a certain percentage of cases that tend to collapse at the close of an extreme test. In our series the test was pushed beyond the usual limits, in fact to the point of inefficiency of the nerve reactions represented by impending or actual unconsciousness.

With the onset of collapse the heart rate suddenly slows. The electrocardiogram proves that the slowing is due to disturbance and suppression of function of the S-A node with temporary persistence and dominance of the rhythm by the A-V node. Conduction is also depressed if not lost as between the two nodes but not distal to the A-V node at this stage of oxygen-want. In one test complete dissociation occurred. The auricular rate was slower than the ventricular, a phenomenon not present in the usual type of heart dissociation. Complete loss of the P wave, the evidence of auricular contractions, occurred in two extreme tests. Irregularities of heart rhythm and in the point of origin of the beat were developed in at least one striking case. We conclude that extreme oxygen-want in man depresses the rhythm and the conduction in the heart and that the basal or sinus-auricular region is the most sensitive, both as to rhythm production and conduction. The mechanism is sensitive to oxygen-want in the base-apex, i.e., the auricle-ventricle direction—a point of phylogenetic significance. Doubtless the same loss holds in oxygen-want in diseases as in these normal healthy men.

Relation of catalase to heart activity. R. J. SEYMOUR.

Determinations were made of the catalase content of the ventricular muscle of turtle hearts which were beating at various rates as the result of exposure to various degrees of temperature. Hearts were warmed and cooled both in situ and isolated and were then tested for catalase content. The results of such determinations showed no relationship between the heart rate and catalase content.

Removal of the duodenum. F. C. MANN.[1]

The investigation was undertaken for the purpose of determining the effects of the removal of the duodenum. Previous work on the problem was reviewed. The anatomy, physiology and pathology of the duodenum and their relation to the extirpation of the organ was discussed. A one-stage operation for the removal of the duodenum was described.

The duodenum was removed from the dog, cat, hog, goat and monkey although in only the first three species has the operation been sufficiently successful to warrant conclusions. Careful studies on the dog did not reveal any noticeable changes following the duodenectomy. Some of the animals have remained in good condition for many months, and one for more than a year. In all instances in which the animal did not do well, some complication has been responsible and not the loss of the duodenum.

Examination of the blood showed it to be normal with regard to cell-counts, hemoglobin, carbon dioxide combining power and hydrogen ion concentration. None of the animals have developed glycosuria. X-ray examination has shown the course of standard barium meal to be practically the same as in the normal dog. Gastric secretion also seems to be normal. Removal of the duodenum in the hog has not prevented normal development nor normal accumulation of fat. The cat also remains in a seemingly normal condition after duodenectomy.

No data have been secured to show that the duodenum is of great importance in any of the species used.

The interpretation of certain muscle phenomena in terms of "all or none." THEO. KRUSE.

The interpretation of certain muscle phenomena in terms of "all or none" is based on the conception that only a limited number of fibers contract with weak stimuli. As the current is increased, more fibers become involved but the intensity of contraction of any individual fiber may be considered the same in either case.

According to this conception the height of contraction in a given state is largely dependent upon the number of fibers stimulated. Certain changes in the time relations with varying stimuli are in part due to the resistance of the non-contracting fibers. Certain changes in the time relations with varying loads are of a character similar to changes produced by weak stimuli. The principal manifestation of this change

[1] Preliminary report of this work has previously been made by F. C. Mann and K. Kawamura, Journ. Amer. Med. Assoc., September 20, 1919.

is a prolongation of the contraction phase so measured from the point of stimulation.

Changes in the relaxation phase due to tonus following weak stimuli may be quickly eliminated by immersion in a cocaine solution while tonus produced by strong stimuli, presumably affecting more internal fibers, may not be removed for much longer periods of immersion. The diffusion time of cocaine is believed to account for this variation.

The application of the "all or none" principle is of distinct value for the interpretation of the state of the tissue and certain changes produced by experimental procedure and by drugs. Such consideration, however, should not minimize the importance of other factors.

Heat production in turtle's cardia in response to stimulus through vagus nerve. CHARLES D. SNYDER.

To avoid error introduced by heat of electrical origin inevitable when smooth muscle is tetanized directly, a vago-cardia preparation of turtle's stomach is isolated and mounted in the muscle chamber for determination of heat production.

An insert thermopile of 30 iron-constantan junctions is used in series with low resistance D'Arsonval, whose sensitivity (1 mm. deflection at 1 M. distance) is 1×10^{-9} amp. of current. Theoretical thermometric value of 1 mm. deflection equals galvanometer sensitivity divided by amperes developed by difference of 1°C. between cold and warm junctions of thermopile, the latter in series with galvanometer of 12 Ω plus necessary additional resistance required for critical damping (16Ω). That is, in the present case

$$1 \times 10^{-9}. \quad \frac{12 + (12 + 16)}{30 \times 53 \times 10^{-6}} = 2.5 \times 10^{-5} \text{ °C.}$$

The period of the galvanometer is 19 seconds, but is not too slow for smooth muscle of cold-blooded species.

As satisfactory experiments I report the two following:

Experiment of 12/1/19. Vago-cardia preparation; weight, 5.3 grams. Of muscle coats, only ca. 2.7 grams. Isotonic lever weight lifted by muscle in all cases 20.7 grams. Preparation left with mucosa inside, thus in direct contact with "warm junctions" of thermopile. "Cold junctions" covered with stomach muscle strips. Temperature of muscle chamber ca. 20°C.

NUMBER OF TRIAL	DISTANCE OF SECOND COIL	STIMULUS	RISE OF CARDIA TEMPERATURE	CALORIES PER GRAM MUSCLE AND GRAM TENSION, ROUGHLY ESTIMATED
	cm.	*seconds*	*deg. C.*	
1	8	17	0.00165	0.00018
2	(Spontaneous contraction)		0.0017	0.00019
3	8	16	0.0014	0.00015
4	6	22	0.0005	0.00005
5	4	24	0.0016	0.00017
6	2	42	0.0017	0.00019
7	0	22	0.0016	0.00017

Experiment of 12/6/19. Vago-cardia preparation. Cardia everted. Weight, ca. 3.7 grams. "Cold junctions" covered with strips of stomach muscle without mucous coat. Isometric lever with Ludwig vertical writing-tip.

NUMBER OF TRIAL	DISTANCE OF SECOND COIL	TIME OF STIMULUS	MECHANICAL TENSION	RISE OF CARDIA TEMPERATURE	CALORIES PER GRAM MUSCLE; PER GRAM TENSION, ROUGHLY ESTIMATED
	cm.	*seconds*	*grams*	*deg. C.*	
1	8	24	13	0.0077	0.00095
2	8	33	28	0.02	0.00116
3	6	28	35	0.0083	0.00044
4	5	18	32	0.003	0.00112
5	6	21	32	0.0029	0.00101

In the two experiments here reported it will be seen that the cardia of the turtle when stimulated through its nerve exhibits a rise of temperature from 0.0001°C. per gram tension exerted in the one case, to 0.0001° or 0.0007°C. in the second case.

Whether the heat necessary for this is developed in the contracting muscle or whether a part or all of it is produced in the gastric glands of the mucosa which also are probably stimulated to activity by the fibers in the nerve trunk, cannot be stated at present with certainty and is a point that must be determined and taken into account before any further conclusions are drawn. Inasmuch as the rise of temperature at the thermocouple junctions was greater in the case where the stomach ring was everted (exper. of 12/6/19), it may be inferred tentatively that the muscle of the cardia is the greater source of heat.

Some remarks on catalase. THEO. C. BURNETT.

A brief review of the recent work of Burge and his collaborators is given, and the criticisms that have appeared. His theory that catalase is secreted by the liver and is responsible for oxidations is not proved. Some observations on the effect of ether on blood show that contact of fluid ether with blood is not destructive of catalase. It is suggested that catalase is a constituent of the cell itself, and varies in its composition and activity in different tissues, as shown in preparations made after the method of Batelli and Stern.

Further studies on excitation of infections of the throat. STUART MUDD, SAMUEL B. GRANT and ALFRED GOLDMAN.

In experiments reported last spring it was shown that chilling of the body surface causes vasoconstriction and ischemia—not, as formerly assumed, congestion—in the mucous membranes of the human palate, faucial tonsil and pharynx. In this respect these membranes and the skin evidently function similarly in heat regulation.

The chief method employed has been direct measurement of variations in temperature in the exposed mucous and cutaneous surfaces by

thermopiles applied by means of galvanized iron "applicators." The applicators in the early work were strapped in position with adhesive tape. In the present experiments they have been held stably in place by a specially devised holder; the wire applicator is held by a set screw in a groove borne by a metal spheroid which is attached by the blades of a head mirror to a second spheroid screwed into one arm of a Doyen mouth gag held between the subject's teeth. Stability and ease of adjustment are thus attained.

Although skin and mucous membranes become ischemic together on chilling the body surface, differences have been shown to exist in their reactions to rewarming. The skin returns to a little above its initial temperature; palatine and pharyngeal membranes have remained somewhat ischemic; the tonsillar temperature has risen well above its level of before chilling.

It seems possible—although this is mere speculation—that this tonsillar hyperemia is an adaptation secondarily acquired as a protection against the organisms always present upon the delicate epithelium of the tonsillar crypts.

With inhalation of amyl nitrite, skin temperature has always shown a sharp transient rise. The mucous membranes, if relatively ischemic, show a rise parallel to the skin. If already hyperemic, local vasodilation in the mucous membrane with amyl nitrite is more than counterbalanced by the lowering of general blood pressure, and temperature falls.

Daily bacteriological cultures were made from the subject's nose, pharynx and tonsils. The nasal flora was sparse and unaffected by the experiments. In three instances a chilling experiment was followed by marked relative increase in the numbers of one microörganism in the throat, the remaining flora remaining apparently unaltered. In one subject Streptococcus hemolyticus proliferated; in a second, Micrococcus catarrhalis; in a third, B. influenzae. The first two instances were synchronous with the appearance of a clinical sore throat; in the case of B. influenzae there were general malaise, slight headache and chilliness, without local symptoms.

Chilling in these experiments by exposing the bared body to an electric fan for 5.5 to 28 minutes in a room of 16.9 to 20.9°C. failed in any case to produce albuminuria or glycosuria. However, a urine more dilute than before the experiment was excreted. The reaction of the urine was usually changed from acid to alkaline; this, on further analysis by Grant and Goldman, was found to be referable to the long period of forced respiration in each experiment.

The experimental production of edema as related to protein deficiency. EMMA A. KOHMAN.

Denton and Kohman,[1] while working on the dietary qualities of carrots, found that dropsy occurred in a large percentage of rats fed on

[1] Denton and Kohman: Journ. Biol. Chem., 1918, xxxvi, 249.

a carrot diet, when the proportion of nitrogen had been reduced by the addition of some nitrogenous foodstuffs, such as fat or starch. A study of the etiology of this edema was undertaken. The study was made upon rats. Diets deficient in protein, in calories, in fat-soluble-A and water-soluble-B except as they came from the carrots, and deficient in fat, respectively, were fed. Diets of high and low water content and of high and low salt content and of an increased acid content were fed.

The following observations were made:

1. When young rats are fed diets composed largely of carrots and with carrots as the only source of protein, a large percentage of the rats develop edema.

2. Fats or fat-soluble-vitamine do not prevent the occurrence or decrease the percentage of edema in rats, even if 10 per cent of the calorie value of the diet is made up of butter-fat.

3. The water-soluble-vitamine does not prevent the occurrence or decrease the percentage of edema in rats fed the low protein diet.

4. Salts do not play any appreciable rôle in the production of this type of edema, for even when the salt content is doubled there is no noticeable effect upon the occurrence of edema.

5. The water intake of the animal which is feeding on the low-protein-carrot-diet decidedly influences the development of the edema. Edema develops more frequently, is more severe and develops sooner on a wet diet than on a dry diet.

6. When a sufficient amount of an adequate protein is added to the low-protein-carrot diet, in place of an equivalent amount of corn starch, edema is not only averted in rats feeding on this diet but the rats show normal growth and reproduction.

7. That the edema does not develop as a result of some toxic substance in the carrots is shown by the fact that rats fed on the control diet with the same carrot content as the low-protein-carrot-diet but with adequate protein did not develop edema and showed normal well-being.

8. When the acid content of the diet was increased the percentage of rats developing edema was increased from 50 per cent to 80 per cent. That the acid in this diet was not the chief etiological factor of the edema is shown by the fact that one rat on this diet was cured and made to grow normally on the diet with no change in the acid content but with an adequate protein supply replacing an equivalent amount of corn starch in the diet.

9. The edema manifested in these rats is not due to simple starvation, or low calorie intake, for when rats are fed a diet, including 1 gram of adequate protein each day, of the same calorie value as the diet fed the edematous rat, they do not develop edema.

10. This edema can be successfully cured by supplying the diet with adequate protein. Edema was produced and cured three times in one rat by alternating low-protein diet (edema producing) with an adequate protein diet.

11. These findings warrant the general conclusion that if it is necessary to limit the amount of protein in a diseased condition or in a period of national economic stress (as was necessary in some of the European countries during the recent war), it is advisable to administer the low-protein diet in a form free from excess of water and any acid-producing foods. Symptoms of developing edema must be looked for and adequate protein supplied immediately to effect a cure.

On the origin of the muscular tremors, clonic and tonic spasms in parathyroid tetany. A. B. Luckhardt, M. Sherman and W. B. Serbin.

Our dogs suffered parathyroidectomy after the animals had fully recovered from transection of the cord at various levels as gauged by the condition of the animal, the wound, and the reappearance of the several spinal reflexes.

Recalling the fact that the neuromuscular phenomena without spinal transection are less severe in the hind than in the fore limbs we record our observations, in general, as follows: *a*, The fibrillary contractions occur in the musculature posterior to the transection; for they may be present in the hind limbs independently of the fore limbs; and they persist in the hind limb isolated, as far as the musculature is concerned, from the remainder of the body; *b*, The clonic spasms, likewise, persist; *c*, The tonic spasms are less pronounced. The tonic spasms, when present, are in a great measure due to the stimulation of sensory nerves of some part of the animal posterior to the transection.

There is a great increase in the reflex irritability of the animals just prior to and during the attack of tetany followed by a corresponding nervous depression after subsidence of the attack; for *a*, removal of the parathyroids simultaneously with spinal transection leads to an earlier return of the reflexes and thus cuts short the period of spinal shock; *b*, during an attack of tetany the reflexes are all exaggerated and some appear pro tempore which have not been seen before or after the attack; *c*, lack of reciprocal inhibition in the patellar phenomenon during the attack of parathyroid tetany points in the same direction.

With small graded doses of strychnine a condition can be produced in an animal indistinguishable from an attack of parathyroid tetany. Again, parathyroidectomized animals are, early during tetany, more susceptible to strychnine than before the parathyroids are removed.

Two dogs which had suffered extensive unilateral extirpations of the cerebellum some 5 weeks previously showed tonic extensions of the limbs of the homolateral as well as the contralateral side during an attack of parathyroid tetany in one instance. In the other dog the fore leg of the homolateral and the hind leg of the contralateral side were tonically extended. The tonic spasm is not as sustained as on the contralateral side. The cerebellar arc seems, therefore, to reinforce but not initiate the tonic spasm. Fibrillary contractions and clonic spasms occur equally well on both sides of the animal (fore and hind limb).

Some observations on dark adaptation of the peripheral retina. M. DRESBACH, JOHN E. SUTTON, JR. and S. R. BURBAGE.

The object of this report is to present some observations made on the course of dark adaptation in the peripheral retina and on the mooted question of regional differences in the retina's sensibility. A flash method was used, permitting of quantitative expression of the sensibility at any moment. The size of the field ranged from 1 to 10 degrees. The nasal and temporal regions in the horizontal plane were most frequently studied, but fields in various other meredia were also stimulated. These areas were located generally 10 or 15 degrees from the fovea. It was found that when the normal retina is well adapted to daylight and the light is suddenly and completely shut off, the sensibility, measured within a half-minute thereafter is already rapidly rising. It is doubled or trebled within the first two or three minutes, then there follows a retardation for three to six minutes, during which time fluctuations in the threshold occur. At the end of six to ten minutes, on the average, in the individuals studied, the curve abruptly rises and continues to ascend, generally with irregularities, for about an hour. We have not been able to show much increase beyond that time. The rate at which the curve rises to the maximal point varies in the same individual on different days and it varies in different individuals. Often there is a marked decrease in the sensibility at the end of an hour, or sooner. Marked fluctuations may occur at any time during the observations and these fluctuations cannot always be ascribed to fatigue, autokinetic sensations associated with fixation of the eye in total darkness or other disturbances commonly met with in work of this character. They seem to be due to actual changes in sensibility of the cerebro-retinal apparatus.

Regional differences in sensibility exist. The difference between the nasal and temporal sensibility in equal fields 15 degrees from the fovea, e.g., may amount to as much as 60 per cent at any instant. At another time the same regions in a given individual may have the same threshold value.

Paradoxical pupil dilatation following afferent path lesions. JOSEPH BYRNE.

All previous contributions refer to efferent path lesions. In the present studies paradoxical effects were elicited by adrenalin intravenously, death, asphyxiation, etc., as follows: (1) In the contralateral pupil after *a*, section or alcoholic injection of one sciatic nerve; *b*, section of dorso-spinal roots Lvii-Sii; (2) In the homolateral pupil after *a*, hemitransection of the spinal cord in upper or lower cervical, or in lower thoracic or upper lumbar segments; *b*, section or alcoholic injection of the brachial plexus; *c*, section of the posterior spinal cervical roots. Paradoxical effects are not abolished by cord transection just above or below the upper thoracic segments, nor by section of the cervical sympathetic, and are not prevented from appearing by cervical cord transection. After sciatic section, etc., paradoxical effects may be elicited from about the 8th to the 15th day, being maximally in evi-

dence about the 12th day. Conclusions: (1) As the histological changes, degenerative and regenerative, that take place in the dorsal root ganglia after sciatic section closely coincide in time and extent with the appearance and disappearance respectively of the paradoxical pupil phenomena, it seems these latter are conditioned by the functional activity of the neurone bodies of the dorsal root ganglia and more especially of the smaller neurone bodies which give origin to the unmyelinated, pain-bearing fibers of the peripheral nerves. (2) From all regions of the periphery in the waking state a flow of afferent impulses impinges on the upper thoracic segments conditioning the efferent flow from the cord to the dilator pupillae. (3) The efferent flow from any region of the periphery probably affects both pupils but because of unequal anatomical distribution one pupil is more affected than its fellow. (4) No evidence has been found of the existence of cerebrospinal dilator pathways in the cervical spinal cord.

A comparison of the physiological effects of alpha and beta rays. ALFRED C. REDFIELD.

A study of the effects of alpha rays from radium upon the egg of Nereis limbata indicates that there are no fundamental changes produced by alpha rays which are not also produced by beta rays. Differences in the effects of alpha and beta radiation can satisfactorily be explained by differences in their penetrating power. Whereas the beta ray passes through the egg with slight loss of energy, and acts with almost equal intensity on all parts of the cell, the alpha ray is completely absorbed before passing two-thirds of the way through the egg, and acts with far the greatest intensity upon the surface layers of protoplasm on the side of incidence. Consequently changes in the process of jelly secretion and membrane formation are limited to the side of the egg exposed to alpha rays.

Unfertilized eggs may be activated with alpha rays, but not with beta rays. This difference is explained by the fact that in the case of alpha radiation the cytolytic action of the rays is limited largely to the cortex, while the interior of the cell is little damaged. With beta rays the interior of the cell is killed before cortical cytolysis has proceeded far enough to induce activation.

Eggs exposed to a mixed beam of alpha and beta rays are killed only slightly more readily than if the alpha rays are excluded from action by means of a suitable filter. This is because the alpha ray effects are sharply localized at the point of absorption and the protoplasm which is not reached by alpha rays survives unless the accompanying beta radiation is strong enough to kill it.

Microdissection studies on the fertilization of the starfish egg. ROBERT CHAMBERS.

When removed directly from a ripe ovary the egg of the starfish possesses a large spherical nucleus or germinal vesicle. After the egg has stood for a while in sea water the boundary of the nucleus fades from view and the nuclear sap begins to diffuse throughout the egg

substance. A small remnant of nuclear material persists as the definitive egg nucleus which produces the polar bodies and, upon fertilization, unites with the sperm nucleus to form the segmentation nucleus.

It has been shown that non-nucleated fragments of the egg in the germinal vesicle stage are non-fertilizable. On the other hand, any fragment of an egg in which the germinal vesicle has disappeared will admit sperm and undergo segmentation.

The experiments recorded here constitute an attempt to trace the distribution of a substance which is necessary to render the egg fertilizable and which appears to emanate from the egg nucleus.

Non-nucleated fragments were cut from eggs in the various stages of the disappearance of the germinal vesicle and sperm was added. The ability of the fragment to approximate regular segmentation was in direct proportion to the amount of intermingling of nuclear sap and egg substance before the fragment was cut off. The later the stage in the disappearance of the germinal vesicle the less irregular is the segmentation of a fragment.

This substance which renders the egg capable of fertilization finally accumulates in the periphery of the egg. It was possible to tear the surface layer of the egg and to cause almost all of the internal protoplasm to flow out through the tear and form itself into a spherule which pinches off from the rest of the egg. The remnant, consisting largely of the more solid ectoplasm, tends only slowly to round up. The extruded very fluid mass immediately assumes an almost spherical shape. This may be termed the endoplasmic sphere. The fragment consisting of the ectoplasmic remnant is readily fertilizable and undergoes normal segmentation. The endoplasmic sphere is non-fertilizable no matter whether it contains the egg nucleus or not.

If the endoplasmic sphere remains connected for some time with the ectoplasmic remnant, it is fertilizable. The ability of the endoplasmic sphere to approximate normal segmentation is a function of the length of time that it remains in continuity with the original ectoplasmic mass. This is intelligible by assuming that the substance which renders the egg fertilizable tends to distribute itself over new protoplasmic surfaces.

The conclusion is that a substance emanates from the germinal vesicle or nucleus of the immature egg, diffuses gradually throughout the substance of the egg until it accumulates in its periphery and on long standing in sea water may be lost from the egg. The presence of a sufficient amount of this substance in the protoplasm of the egg is necessary to fertilization.

Susceptible and resistant phases of the dividing sea-urchin egg when subjected to various concentrations of lipoid-soluble substances, especially the higher alcohols. FRANCIS MARSH BALDWIN.

When subjected to suitable concentrations of various lipoid-soluble substances—i-amyl, hexyl, heptyl, octyl and capryl alcohols—the developing sea-urchin egg shows unmistakable rhythms of susceptible and resistant phases, which facts when taken in connection with the

earlier observations of Lyon, Herlant, Mathews, Spaulding, Lillie and others, constitute additional evidence that a very intimate relation exists between the general physiological condition of the egg and the physical state of its plasma-membrane. During the first few minutes (ten to fifteen minutes after fertilization) the eggs are more susceptible to all substances tried than at any other time until the period just preceding and during the division process. A comparatively resistant phase gradually becomes more and more evident up to just before the cell-division (between forty-five and forty-eight minutes after fertilization). A period of marked increased susceptibility occurs during the division process which outlasts the furrow formation in most cases by several minutes (some instances by as much as ten or fifteen minutes), and during this interval marked cytological effects in the eggs are noted. Subsequently the resistant phase is largely recovered, and is then maintained to a greater or less degree up to the time of the second cleavage.

The most favorable concentrations of the various alcohols for demonstrating the rhythmical relations range as follows: i-amyl, between 0.7 and 0.9 vol. per cent; hexyl, between 0.13 and 0.17 vol. per cent; heptyl, between 0.06 and 0.07 vol. per cent; normal octyl, about 0.015; while capryl was considerably above its isomere (normal octyl), in toxicity varying in range between 0.035 and 0.045 vol. per cent. The best records were obtained using i-amyl and capryl alcohols, possibly indicating a higher specific toxicity of these when compared to the others. When suitable concentrations were used, no marked differences could be detected by varying slightly the durations of exposure. Eggs exposed for five, eight or even ten minutes to the same concentration gave similar results when referred to survivors. This however would apply only within comparatively narrow limits. Data when plotted with reference to survivors and time exposures respectively give typical reversible curves in practically all cases.

Effect of breathing dry and moist air. E. P. Lyon and Esther Greisheimer.

The air surrounding the body of human subjects was kept constant in temperature and humidity, while these subjects for 10 to 15 minute periods breathed air of constant temperature but varying humidity. Temperature of room, 20 to 22°C., humidity of room, 50 to 60 per cent. Temperature of air breathed 20° to 30°C. in different experiments; humidity of air breathed, about 10 per cent and 90 per cent respectively. Tentative results: higher pulse rate, lower respiration rate, higher arterial pressure, greater peripheral vascularity in breathing moist air than in breathing dry air.

Acidosis a criterion of surgical shock. Bernard Raymund.

The work here summarized is an attempt to determine whether there might be a so-called shock level in the alkali reserve, such as would constitute, in experimental work, a useful criterion of surgical shock.

Experimental procedures were those commonly employed. Dogs under ether anesthesia were brought into a state of shock by gentle manipulation of the intestines for short periods of time only. The criteria for shock used were those proposed by Mann in 1914 and since generally adopted. The following conclusions were arrived at:

1. The normal alkali reserve of the dog, as determined on the venous plasma by the Van Slyke method, varied between 32.4 and 59.5 volumes per cent, corrected The mean of sixty-two determinations was 42.7 volumes per cent.

2. The effect of etherization was to cause a mean fall in the alkali reserve of 10.5 volumes per cent from the normal. If etherization is prolonged up to three hours the mean fall from the normal is 21.2 volumes per cent. Control experiments showed that there is not much further change in the alkali reserve if etherization is prolonged still further. Thus after ten hours of continuous ether anesthesia one dog showed a fall in the alkali reserve of 13.8 volumes per cent, while another showed a fall of 25.6 volumes per cent. These figures all refer to the arterial plasma.

3. The dogs used could be classified on the basis of the length of time they survived after trauma was begun. Thus four types of shock were made out, ranging from the more severe, characterized by sudden onset and death, to that in which few or none of the cardinal signs were observed. The majority of the dogs showed the intermediate types, living from two hours (type II) to four hours and a half (type III) after beginning trauma.

4. When shock ensued suddenly the fall in the alkali reserve was relatively insignificant. When shock was slow in appearing the alkali reserve might remain high for some time, not falling until after the condition of the dog had become quite grave. There was no correlation between the degree of this fall and the type of shock; nor could the resistance to trauma be predicted from the dog's initial alkali reserve.

5. Our experiments showed further that the alkali reserve may fall no lower in shock than in previously conducted ether controls from which the dogs make good recovery.

6. Thus there is no critical level for the alkali reserve *of the blood* in relation to traumatic shock.

7. None of the signs of shock were shown by dogs or cats given lethal injections of acid or acid phosphate.

Further results on the physics of sphygmography. A. M. Bleile and Clyde Brooks.

The Riva-Rocci and similar types of sphygmomanometers contain certain elements of construction which do not permit the determination of systolic and diastolic pressure by direct reading of the manometer oscillations.

One factor lies in the large volume of air in the cuff relative to the small volume of displacement possible by the restricted brachial artery. The compressibility of the air and consequent change in volume would

set a limit to pressure given by the manometer which is dependent on the possible limited change in the volume of the artery rather than on the pressure itself. Boyle's law PV = K where P = pressure, V = air in the cuff and K the resulting constant, applies here. P being large (750 mm. atmos. pressure and say 100 mm. added = 850). V being large, usually about 200 cc. or 200,000 cu. mm. the product would be 170,000,000. Now $P = \frac{K}{V}$ and the pressure obtainable by pulsation of the brachial would at the most be the addition of the volume of that artery which, assuming a diameter of 5 mm., length of cuff of 100 mm., would be about 2,000 cu. mm. which sum only would be subtracted from the divisor thus giving a relatively small possible difference.

Even without this theoretical treatment the general fact was recognized and this led to other methods than direct reading of the manometer such as interpretations of the extent of the oscillations, the determinations of pressures at the extinction of the radial pulse and its reëstablishment by palpation and, later, by determining these points by the auscultation with a stethoscope placed over the brachial artery just below the cuff. Without discussion of these methods we offer another which seems to have certain advantages. The cuff is filled with water, a non-compressible fluid as compared with air; one tube of the cuff is connected with a three-way tube again uniting into a single arm connected with the manometer. One branch of the tube when open gives the ordinary manometric readings, if its valve is closed to a capillary opening the mean arterial pressure is given. Another branch carries a valve opening to the manometer and with this tube open the maximum or systolic pressure is given. The third branch carries a valve opening from the manometer toward the cuff and when this is open the minimum or diastolic pressure is obtained. All pressures are of course influenced somewhat by the resistance of the overlying tissues. The cuff is filled with a pressure bottle which can readily be lowered thus taking off the pressure when discomfort is felt by the subject and raised after recovery without derangement of the apparatus, thus making long observations possible.

The influence of internal secretions on blood pressure and the formation of bile. ARDREY W. DOWNS.

A study was made of the effect of intravenous injections of the following gland substances on blood pressure and the formation of bile: Mammary, orchic, ovarian, pancreatic, splenic, thymic and thyroid. To this list was added secretin and solution of adrenalin chloride.

As the result of these experiments we believe that some at least of the endocrine organs exert a specific influence on the secretory activity of the hepatic cells leading to the production of bile. The output of bile in the dog is increased by the administration of secretin. It is decreased by the administration of adrenalin, and by mammary, orchic, ovarian, pancreatic and thymic gland substances. It is not affected in a constant or definite manner by the substance of the spleen

and thyroid gland. Blood pressure is raised by adrenalin and lowered by pancreatic substance and the secretin preparation employed. A fall of blood pressure, ordinarily preceded by a slight rise, is caused by orchic and mammary gland substances. Oscillations of blood pressure are caused by ovarian and thyroid gland substances. Blood pressure is not usually affected by splenic and thymic gland substances.

While the experiments are too few in number to permit definite conclusions to be drawn yet it seems certain that there is no constant relation between blood pressure and the amount of bile secreted. Adrenalin consistently raised blood pressure and lowered bile formation. Secretin, where it caused a change in blood pressure, produced a lower pressure and a great increase in the flow of bile. It might be urged that thyroid gland substance owes any action it exerts upon blood pressure and bile formation to the intervention of the adrenals; this cannot be entirely controverted by our experiments. That thyroid substance increases the output of adrenalin has been shown by Bückner,[1] Rudinger, Falta and Eppinger[2] and Gley and Quinquaud.[3] In our experiments there is no constant relationship between blood pressure and bile production after the administration of thyroid gland substance. We did not find bile production regularly decreased when blood pressure rose or vice versa. Intravenous administration of the substance of the pancreas caused lowering of the blood pressure and lessening of the output of bile. To a lesser extent thymic substance acted in the same manner. If we place in contrast with this the effect of secretin it would seem that we are not justified in concluding that the effect on bile formation is due to the alteration in blood pressure.

The blood in clinical shock. G. C. Weil and C. C. Guthrie.

These studies are an extension of the blood studies in experimental shock, previously reported.

The material has consisted of seven patients admitted to the hospital following traumatic injury, as gun shot wounds or crushing of the limbs, and one post-operative case. The clinical symptoms of those in shock varied from mild to the most pronounced, death occurring in some instances.

Blood samples were taken by ear puncture and from an arm vein by means of a syringe.

Red cell counts were of subnormal to normal range. Ear samples (by puncture, i.e., capillary) ranged slightly lower than venous.

Hemoglobin (by Sahli's method) was concordant with red cell counts. This was the case also for the hemoglobin content of venous blood as calculated from the oxygen capacity (Van Slyke's method).

Plasma bicarbonate (by Van Slyke's method) was in the upper limits of the subnormal range.

[1] Bückner: Compt. rend. d. l. Soc. d. Biol., 1908, lxiv, 1123.
[2] Rudinger, Falta and Eppinger: Zeitschr. f. klin. Med., 1908, lxiv, 1.
[3] Gley and Quinquaud: Compt. rend. Acad. d. Sci., 1913, clvi, 2013.

Conclusions: The results accord with previous experimental findings,[1] namely, as indicated by red cell count and hemoglobin concentration, the blood was of subnormal to normal dilution.

The plasma bicarbonate content was moderately diminished.

Causatively, blood changes are not considered significant.

Drs. W. S. McEllroy and T. K. Kruse are associated with us in this work.

A method for determining the rate of oxygen absorption by blood. W. S. McEllroy and C. C. Guthrie.

Blood from influenzal cases was observed to be of dark color and, as judged by the hue, resistant to oxidation on exposure to air. Addition of serum from the same blood accelerated arterialization but not so greatly as normal serum. In serum of some bloods of this type methemoglobin was detected spectroscopically. It was considered desirable to determine if the phenomenon was related to possible deficiency in in oxygen-transmitting capacity of the serum.

The method presented has been developed from this standpoint, with particular reference to the rate of oxygen absorption. Briefly, it consists in reducing blood (1 cc.) to approximately normal venous oxygen content by means of a partial vacuum, and then continuously shaking it in a closed air chamber until it is saturated. Changes in volume of the air in the chamber are followed by frequent readings of a delicate manometer. Quantitatively, the results closely agree with direct oxygen content determinations (by Van Slyke's method), and the curves, plotted from the readings, correspond well with curves of the rate of absorption established by other methods. Control tests show comparatively small differences.

The method is in the experimental stage and, therefore, all factors concerned have not been evaluated, nor its value and limitations established, but the results encourage further study.

Further studies on the action of acacia and associated colloids. Theo. Kruse.

1. The agglutination of human blood by gelatin and acacia is equally intense and is only slight with soluble starch.

2. Evidence was presented showing that agglutination by certain colloids seems to be a function of the aggregate and seems less apt to be due to a possible impurity unless its presence is proportional to the concentration of the aggregate.

3. Reasons were presented which seemed to explain the failure of agglutination of ox corpuscles by the more fixed condition of their surface charges.

[1] Guthrie and Guthrie: Proc. Soc. for Exper. Biol. and Med., 1914, xi, 148.
Guthrie: Proc. Amer. Physiol. Soc. for 1917; Journ. Amer. Med. Assoc., 1917, lxix, 1394; Arch. Int. Med., 1918, xxii, 1.
McEllroy: Journ. Amer. Med. Assoc., 1918, lxx, 846.
Mummery and Symes: Journ. Physiol., 1907, xxxvi, xv; British Med. Journ., Sept. 19, 1908.

4. Agglutination is interpreted as an adsorption phenomenon.

5. Experiments on rhythmical tissues with acacia give evidence of adsorption.

6. The current view of explaining colloidal responses in terms of colloidal osmotic pressure was shown to be inadequate in so far as it fails to explain certain facts relating to acacia, gelatin, dextrin and soluble starch.

7. An interpretation based upon adsorption on capillary walls was suggested for consideration since current facts dealing with these colloids are thereby explained.

8. Experiments thus far indicate that such solutions which are recommended to prolong the maintenance of blood volume, apparently do so by an interference with the normal paths of fluid exchange by an adsorption of colloid on capillary walls, and when the concentration of such colloids is of sufficient magnitude to produce this effect agglutination may play a prominent rôle.

Observations on the capillary blood pressure in man with presentation of a new method. D. R. HOOKER and C. S. DANZER.

A method is presented for the study of capillary blood pressure in man. It differs from all of the previous work in the criterion taken for the determinations. This depends on the visualization of the corpuscular flow within the capillary loops of the skin. For this purpose the skin immediately adjacent to the cuticle of the nail is covered with a drop of castor oil and a concentrated light is thrown on this area and the capillaries are observed through the microscope. We have found a magnification of about 70 × satisfactory; this must be had with an objective giving a focal distance of not less than 16 mm.

The apparatus consists of a closed chamber having a glass roof and a floor consisting of loosely tied on peritoneal membrane or goldbeaters' skin, which is soaked in castor oil. The oil makes the membrane soft and transparent. Air is pumped into the chamber until the membrane adheres to the skin. Now the pressure within the chamber is raised until the corpuscles stop. When the pressure is slightly lowered the corpuscles begin moving again. At this point the pressure is read off on a mercury manometer. All of the corpuscular phenomena seen by Roy and Brown on the frog have been observed in man.

The capillary blood pressure was studied in 31 individuals (25 adults and 6 children). It varied between 18 and 26.5 mm. Hg.

The average pressure in a series of capillaries was remarkably constant from day to day, although the pressures in individual capillaries were variable.

Studies on postural variations of capillary pressure exclusive of hydrostatic effect showed the pressure was lowest in the horizontal, highest in the vertical and between the two in the sitting posture.

The effect of temperature was as follows: Local cold produces a fall in capillary pressure followed by a marked rise much above the normal and then a slow return to normal after the cold has been removed.

Local heat causes a rise; on removing the heat the pressure first falls to a subnormal level and subsequently returns to the normal value.

Increased intrathoracic pressure causes a rise in capillary pressure and lessened intrathoracic pressure produces a fall in capillary blood pressure.

The method is simple and can be applied clinically. We propose the name "Micro-Capillary Tonometer" for our apparatus.

Some effects of ether and morphine on the blood and circulation in shock. McKeen Cattell.

The blood pressure of animals in shock becomes very sensitive to the effects of ether and chloroform, the inhalation of an amount insufficient to abolish the eye reflex causing a large drop in pressure. This degree of anesthesia was without permanent effect on the blood pressure of unshocked animals. The same degree of anesthesia produced by nitrous oxide and oxygen in the most favorable proportions (usually three parts nitrous oxide to one of oxygen) given to animals in this condition caused no fall in blood pressure. After a large dose of intravenously injected adrenin the ether fall was much less or entirely absent. Pituitrin was without effect. In this condition of shock after prolonged low blood pressure the vasomotor center is quite insensitive to stimulation by asphyxia, and it is suggested that this increase in ether effect may be due in part to an impairment of the vasomotor center. In the unshocked animal the decreased heart output resulting from the administration of ether may be compensated for by a reflex peripheral constriction. This does not occur in the shocked animal and the pressure continues to fall to zero.

Morphine given in large doses did not accelerate the development of shock produced by reducing the blood pressure to 60 mm. Hg. by means of pressure in the pericardium. Determination of the alkaline reserve at a shock blood pressure did not show the usual fall when morphine was given, or if it was given after acidosis had already developed, the reading returned nearly to normal. The results are summarized in the table, the figures representing the average per cent of carbon dioxide in samples of the blood plasma taken at the times indicated.

	NUMBER OF CASES	DURATION OF LOW BLOOD PRESSURE (60 MM.)			
		Start	1 hour	2 hours	3 hours
No morphine	8	34.7	27.1	26.1	26.1
Morphine after first hour	8	30.1	21.9	23.9	27.6
Morphine at start	6	33.5	32.2	34.0	34.7

The rôle of the vagi and splanchnic nerves in the genesis of shock from abdominal operations. A. C. Ivy.

In dogs, both vagi were cut intrathoracically above the diaphragm and both splanchnics were sectioned and celiac plexus with the ganglion extirpated, thus isolating the intestines from the central nervous system. Such animals, if properly cared for recover quickly and live

in good health. After recovery (four to six weeks) the animals were tested under local anesthesia (novocain-adrenalin). The left carotid was cannulated for blood pressure, the abdomen opened widely and the intestines were vigorously manipulated. No signs of pain were observed except when the mesentery was pulled. Care was taken to avoid this and all other causes of pain. Samples of blood were drawn at intervals from the inferior vena cava by syringe, and hematocrite, hemoglobin, red blood corpuscle count and plasma bicarbonate determinations were made. The body temperature of the animals was followed. The same procedure was carried out on normal controls.

The following observations were made: It was possible to produce shock by vigorously manipulating the intestines of animals in which both vagi and splanchnics had been sectioned and time allowed for recovery from the operation. However, it took from three to five times longer to produce shock in the dogs with isolated intestines than the intact control animals. Also, the fall in blood pressure was much more gradual in the former than in the latter. The blood changes in both series of animals were practically the same as those reported by other observers working on shock. Marked congestion of blood and loss of irritability of the intestine to mechanical stimulation appeared sooner in the control animals than in the animals with isolated intestines.

The conclusion is warranted that the vagi and splanchnics are not directly concerned in the genesis of shock produced by manipulations of the intestines, but the presence of these nerves does hasten the onset of shock.

The chemistry of gar roe. CHAS. W. GREENE and ERWIN E. NELSON. The averages of the results of the analyses of ten samples of the roe of the gar, Lepidosteus platostomus, were given. The water content was found to be about 55 per cent. The water content was found to be highest in the youngest, most immature samples, and was here associated with a high value for the extractive solids, and low values for proteins and lipoids. Conversely, in the older, more mature samples, the water was low, the extractive solids were small in amount, and the lipoid and protein values were high.

The ether-soluble, or lipoid fraction, was found to be high in value, giving an average determination of about 16 per cent, and in one case reaching the value of 28 per cent, which is one of the highest given in the literature. The proteins, determined directly, varied from 15 per cent to 28 per cent, with an average of about 24 per cent.

The extractive fraction was small relative to other tissues or compared with other fish eggs. The total solids averaged about 1.5 per cent, and the ash about 0.36 per cent. The total nitrogen of the extractives varied from 0.05 per cent up to 0.3 per cent, with an average of about 0.16 per cent. Of the total nitrogen, about 20 per cent is found in the alpha-amino nitrogen fraction, the average figure being 0.034 per cent creatin and creatinin determinations gave an average of 0.0073 per cent, varying from 0.0038 to 0.0096 per cent, determined as creatinin nitrogen.

The excretion of a red pigment in the sweat of man. M. H. GIVENS, V. L. ANDREWS and H. B. MCCLUGAGE.

An apparently healthy, well-developed boy, age 10 years, weight 58 lbs., excreted on two occasions perspiration which contained a red pigment. Two years intervened between attacks and the duration of each was about ten days. The first attack occurred in the month of May and the second in October, the weather being rather warm each time and favorable for one to perspire.

The pigment was excreted in the sweat appearing around the left eye and down onto the cheek bone. If perspiration was evoked by either exercise or the application of heat the pigment was produced. Removing the pigment with water and subjecting the face to dry heat from an electric stove for six consecutive times markedly diminished the output of pigment. A rest of twenty-four hours sufficed to permit a new accumulation of material. The pigment colored the face a bright red resembling a smear of blood.

The dye as excreted was soluble in water and dilute alkalies and insoluble in dilute acids and ether. Addition of dilute hydrochloric acid to the face washings precipitated the dye which could then be dissolved in ether. By this procedure a small amount of material was purified. On evaporating the ether a dark red volatile oily substance was obtained. This purified material contained no nitrogen and left no residue on igniting. No phenol grouping could be detected. With 30 mgm. of material a neutral equivalent of 466 was obtained.

The possibility that diet may have played some rôle in this peculiar metabolic disturbance cannot be overlooked. At the first attack the boy had a marked craving for and consumed a large amount of lemons and at the second one there was a desire for and large amounts of tomatoes eaten. On the assumption that a large intake of organic acids might stimulate a production of the pigment, a short intensive feeding of lemons was tried after the color had ceased to appear. Negative results were obtained within the short experimental period.

Vascular reaction to epinephrin in perfusates of various H-ion concentration. CHARLES D. SNYDER and W. A. CAMPBELL, JR.

Reversal effect of epinephrin (Hoskins, 1912; Cannon and Lyman, 1913) was observed by Snyder and Andrus (Journ. Pharm. Exper. Therap.) when the drug was applied to isolated turtle heart. While augmenting tonus already evoked by a Ringer of 7.8 pH index, it still further diminished the atony evoked by Ringer of pH 7.0. This pointed to the possibility of the H-ion concentration as being the reversing agent. To test the validity of this view experiments were planned and some have been carried out as a special investigation.

So far fresh fall frogs prepared for vascular perfusion (Trendelenburg's method) give confirmatory evidence. The dilution of the adrenalin chlorid must be very great. If it is not more than $1:10^7$, only constrictor effects are obtained. We submit the following:

REMARKS	PERFUSION BEGUN AT	RECORD BEGUN AT	pH INDEX	ADRENALIN CONCENTRATION	NUMBER OF DROPS IN ONE MINUTE
Experiment of 11/25. Frog I, pressure, 19 cm. of water.		11:25	7.0	0	22
	11:29	11:34	7.0	$1:10^9$	28
	11:38	11:44	7.0	0	26
	11:47	11:53	7.0	0	26
	11:57	12:03	7.0	$1:10^9$	30
	12:10	12:16	7.0	0	24
	12:19	12:25	7.0	0	22
Experiment of 12/13. Pressure at 18 cm. water.	1:34	1:40	7.2	0	59
	1:43	1:49	7.2	$1:10^9$	72
	1:52	1:58	7.2	0	43
	2:00	2:06	7.2	$1:10^9$	65
	2:09	2:15	7.2	0	60
Experiment of 11/8/19. Eviscerated male, pressure, 10 cm. water column.		11:50 a.m.	7.0	0	2
	11:54	11:59	7.0	$1:10^9$	49
	12:01	12:06	7.0	0	5
	12:08	12:13	7.8	0	2
	12:16	12:21	7.8	$1:10^9$	1 drop in 3 minutes
	12:21	12:28	7.8	$1:10^9$	
	12:31	12:36	7.8	0	2
	12:39	12:44	7.0	0	5
	12:48	12:55	7.0	$1:10^9$	18
	12:57	1:03 p.m.	7.0	0	14
	1:08	1:14	7.0	$1:10^9$	22
	1:19	1:29	7.0	0	19
	1:33	1:38	7.8	0	3
	1:42	1:47	7.8	$1:10^9$	2
	1:50	1:55	7.0	0	32
	1:59	2:04	7.0	$1:10^9$	47

In the experiments of 11/8/19 the reversal effect is most marked —the extreme diminution of outflow during constriction being doubtless due to the low head of pressure used. It will be noted that the same dilution of the adrenalin in Ringer of pH = 7.8 not only gives no reversal (dilator) effect, but even appears to augment the constriction already evoked by the excess of OH-ions.

The effect of the subcutaneous injection of adrenalin chloride on the heat production, blood pressure and pulse rate in man. WALTER M. BOOTHBY and IRENE SANDIFORD.

The results of forty-six experiments on the effect of the subcutaneous injection of adrenalin chloride (0.5 cc. of 1–1000) on the metabolic rate, respiratory quotient, pulse rate and blood pressure, are reported. These studies were made chiefly on groups of patients who showed variations in the activity of the thyroid, pituitary or adrenal glands, as well as a small group of clinical normal controls.

It was found that adrenalin invariably caused an increase in the heat production and in thirty-nine experiments there was an increase in the respiratory quotient. This rise in heat production is accompanied by an increase in the ventilation rate and as a rule by an increase

in the respiration rate, heart beats per minute, volume of each beat, greater utilization of the blood-carrying power and peripheral vascular dilatation with an increased systolic and decreased diastolic blood pressure. Not all these compensatory factors necessarily come into play in each instance. As would be expected, various combinations may occur, sometimes one factor, sometimes another factor acting as the major compensation. The data show that there is no relationship between the character of the adrenalin reaction and the degree of activity of the thyroid gland and, therefore, in our opinion, contrary to that of Goetsch, the reaction is not indicative of the presence or absence of hyperthyroidism.

The similarity of the metabolic rate curve following the injection of adrenalin to that found by Lusk from a carbohydrate plethora naturally directs attention to the possibility that the increased heat production is due to an excess of carbohydrate metabolites. There may be, however, in addition a direct chemical stimulation of cellular combustion.

Further experiments on the effects of warming and cooling the sino-auricular node in the mammalian heart. BENJ. H. SCHLOMOVITZ.

Dogs and cats were used. Tracings were taken by tambours connected with auricle and ventricle, and time with hundredths-seconds tuning fork. The cardiac tissue, mainly sino-auricular node was warmed or cooled by a special thermode.[1] The results are summarized.

1. The primary cardiac pacemaker maintains its normal locus in both light and deeply etherized animals even to the toxic stage of etherization with auricular dilatation, whether atropine has been given or not. The sino-auricular node responds to both warming and cooling.

2. A persistent tachycardia cannot be produced by warming the sino-auricular node for long periods in lightly anesthetized animals, whether atropinized or not. Instead the rate slows after a transitory tachycardia to a rate close to or less than normal, and upon removal of the thermode the rate usually drops below normal. The A_sV_s interval may show no change throughout or after the period of warming, or may decrease 0.02 to 0.03 second gradually, or show no consistent variation.

3. An experimental tachycardia of nomotopic origin with short periods of sudden onset and offset resembling certain clinical cases may be produced. Occasionally, an experimental auricular flutter can be shown.

4. In some cases of advanced digitalization of the heart, when idioventricular rhythm prevails, repeated production of ventricular fibrillation following ventricular tachycardia can be instituted by warming any localized portion of the ventricles. This quickly passes off on removal of the thermode.

[1] Schlomovitz and Chase: Arch. Int. Med., 1917, xx, 613.

Effect of glutamine production on urinary nitrogen. CARL P. SHERWIN, W. WOLF and M. WOLF.

Two men were brought into a condition of minimal nitrogen metabolism by a diet of potatoes, bananas, small amounts of bread, butter and cocoa.

Each man was fed 2.5, 5, 7.5 and 10 grams of phenylacetic acid as a water solution of the sodium salt. Subject no. 1 ingested the acid in single doses while subject no. 2 ingested the acid as 0.5 gram doses at hourly intervals. The phenylacetylglutamine excreted in the urine after the ingestion of the phenylacetic acid was determined quantitatively. Quantitative determinations were also made of total nitrogen, urea, uric acid, creatinine and ammonia.

In subject no. 1 there was an increase in total urinary nitrogen after the ingestion of the acid and a great decrease in the amount of urea nitrogen, a slight increase in ammonia and little or no alteration in the amount of creatinine and uric acid. Subject no. 2 showed a much greater increase in total urinary nitrogen but less alteration in the excretion of urinary nitrogen. Glutamine is produced by the organism in much greater quantities than found in the food. The method of its production is still as uncertain as that of glycocoll.

The rôle of catalase in the animal organism. W. E. BURGE.

Substances such as amino acids, sodium salts of the fatty acids, glycerine and sugar were found to produce an increase in catalase when introduced into the alimentary tract by stimulating the liver to an increased output of this enzyme. When an Eck fistula was established these substances produced no increase in catalase. Substances such as the narcotics which produce a decrease in oxidation were found to produce a decrease in catalase by diminishing its output from the liver and by the direct destruction of the enzyme.

The introduction of chlorine into the methane molecule is known to enhance its effect as a narcotic. It was found that it rendered it more effective in decreasing catalase. The introduction of sodium acetate into the alimentary tract stimulates the liver to an increased output of catalase. The introduction of chlorine into the sodium acetate molecule decreases its stimulating effect on catalase production. The tri-chlorine substitution product of acetaldehyde, chloral, decreases catalase more than does acetaldehyde, a weaker narcotic.

The respiratory quotient and its uncertainty. J. A. FRIES.

If the term *respiratory quotient* when applied to animals refers to the collective exchange of gases due to the metabolic activity of the individual cells forming the body tissues, then a term is needed which will convey that idea.

Because of its great fluctuations during the day the average of a few short period tests does not always represent the daily respiratory quotient. Further the presence of gases of uncertain origin and quantity, such as fermentation gases of the intestines, is also a source of

much uncertainty. With a fasting man in a respiration calorimeter Benedict obtained closely agreeing daily respiratory quotients, average for 7 days being 0.75 and for 3 days with food an average of 0.817. The difference, however, between the 2-hour periods and the average for the same day was as high as 37.18 per cent. In Carpenter's work the same thing is noticed. In very many instances 15-minute tests, not far apart, varied from 9 per cent to 31.4 per cent from each other.

Likewise with the pulmonary respiratory quotient of oxen (Klein), short tests following closely upon each other varied up to 14.3 per cent and the averages of 7 groups of tests as much as 23.2 per cent. Hence duration of tests and volume of accidental gases are deciding factors in a determination.

Markoff gives ratio of CH_4 to CO_2 taken directly from the paunch as 1:3.68 and as 1:5.19 before any absorption takes place. Klein, with oxen during six 24-hour Regnault-Reiset tests, found the daily respiratory quotient = 1.034 and later a pulmonary quotient = 0.882. Mollgaard and Anderson with a milking cow found the pulmonary quotient = 0.967. The writer, with a different method, for milking cows found, using the 1:3.68 and 1:5.19 ratios for CH_4 to CO_2, for cow I, 1.031 and 0.816, and for cow II, 1.078 and 0.856 respiratory quotients respectively.

Methods: Klein used short periods, small samples and pyrogallate; Mollgaard and Anderson long periods, large samples and their hydrogen combustion method; Fries long periods, large samples and his carbon combustion method for oxygen determination.

The present problems are to determine more accurately the ratio of CH_4 to CO_2 produced in the intestinal tract and the amount of these gases passing out through the lungs.

The action of prostatic extracts on isolated genito-urinary organs. D. I. MACHT and S. MATSUMOTO.

The contractions and tonicity of various surviving excised genito-urinary organs were studied in vitro: first, under normal conditions, and second, after the addition of prostatic extracts to the medium in which the tissues were suspended. The following organs were examined: Uterus and Fallopian tube, bladder and ureters, and vas deferens and seminal vesicle. Aqueous saline extracts of the ram's, dog's, bull's, steer's and human prostate glands were used. It was found that all of the above organs are stimulated in vitro by prostatic extracts, provided a sufficient dose is used; but that different organs require different doses of the glandular extract. The uterus and tubes were found to respond to the smallest quantities of prostatic extract; the bladder and ureters came next in the order of their response to such treatment; while the vas deferens and seminal vesicles required the largest doses of the extracts to give evidence of any physiological effect. As a result of the experiments, the authors conclude that the prostatic extracts cannot be regarded as having any specific or marked influence on the tonus and contractions of the bladder in vitro. Fuller data will appear in due time in the Journal of Urology.